3-(1H-INDOL-3-YL)INDAN-1-YLAMINE DERIVATIVES FOR THE TREATMENT OF DEPRESSION AND ANXIETY

FIELD OF THE INVENTION

The invention provides novel indane compounds which are useful in the treatment of depression, anxiety and other CNS disorders.

BACKGROUND OF THE INVENTION

All currently available antidepressants can be classified in 3 classes:

1) monoamine oxidase inhibitors (MAOIs),
2) biogenic amine neurotransmitter [serotonin (5-HT), norepinephrine (NE) and dopamine (DA)] transporter reuptake blockers, and
3) modulators, especially blockers of one or more of the 5-HT and/or NE receptors.

Since depression is associated with a relative deficiency of the biogenic amines, the use of 5-HT and/or NE-receptor blockers (i.e. 5-HT and or NE-antagonist's) has not proven very successful in the treatment of depression and anxiety and the preferred and currently most efficient treatments are based on the enhancement of 5-HT and/or NE neurotransmission by blocking their reuptake back from the synaptic cleft (Slattery, D.A. et al., "The evolution of antidepressant mechanisms", *fundamental and Clinical pharmacology*, **2004**, 18, 1-21; Schloss, P. et al, "new insights into the mechanism of antidepressant therapy", *Pharmacology and therapeutics*, **2004**, 102, 47-60).

Selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they generally are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants. Drugs claimed to be SSRIs are for example flouxetine, sertraline and paroxetine.

However, clinical studies on depression indicate that non-response to the known SSRIs is substantial, up to 30%. Another, often neglected, factor in antidepressant treatment is the fact

that there is generally a delay in therapeutic effect of the SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Furthermore, sexual dysfunction is generally a side effect common to SSRIs. Accordingly, there is a desire for the development of compounds capable of improving the treatment of depression and other serotonin related diseases.

A newer strategy has been the development of dual re-uptake inhibitors, e.g., the combined effect of 5-HT reuptake inhibition and NE (norepinephrine is also named noradrenaline, NA) reuptake inhibition on depression is explored in clinical studies of compounds such as Duloxetine (Wong, "Duloxetine (LY-248686): an inhibitor of serotonin and noradrenaline uptake and an antidepressant drug candidate", *Expert Opinion on Investigational Drugs*, **1998**, 7, 10, 1691-1699) and Venlafaxine (Khan-A et al, 30 "Venlafaxine in depressed outpatients", *Psychopharmacology Bulletin*, **1991**, *27*, 141-144). Compounds having such dual effect are also named SNRIs, "serotonin and noradrenaline reuptake inhibitors", or NSRIs, "noradrenaline and serotonin reuptake inhibitors".

Since treatment with the selective NE reuptake inhibitor reboxetine has been shown to stimulate 5-HT neurons and mediate the release of 5-HT in the brain (Svensson,T. et al, *J. Neural. Transmission*, **2004**, 111, 127) there might be a synergistic advantage using SNRI's in the treatment of depression or anxiety.

The use of SNRI's has been shown in clinical studies to have a beneficial effect on pain (e.g. Fibromyalgia syndrome, overall pain, back pain, shoulder pain, headache, pain while awake and during daily activities) and especially pain associated with depression (Berk, M. *Expert Rev. Neurotherapeutics* **2003**, 3, 47-451; Fishbain, D.A., et al. "Evidence-based data from animal and human experimental studies on pain relief with antidepressants: A structured review" Pain Medicine 2000 1:310-316).

SNRI's have also been shown in clinical studies to have a beneficial effect in attention deficit hyperactivity disorder (ADHD) (N. M. Mukaddes; Venlafaxine in attention deficit hyperactivity disorder, European Neuropsychopharmacology, Volume 12, Supplement 3, October 2002, Page 421).

Furthermore, SNRI's have been shown to be effective for the treatment of stress urinary incontinence (Dmochowski R.R. et al. "Duloxetine versus placebo for the treatment of North American women with stress urinary incontinence", Journal of Urology 2003, 170:4, 1259-1263.)

Naranjo, C. *et al.* " The role of the brain reward system in depression" *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **2001**, *25*, 781– 823 discloses clinical and preclinical findings of links between lack of extra cellular dopamine in the mesocorticolimbic system and anhedonia, which is one of the main symptoms of depression.

Several studies suggest that serotonin and dopamine neurotransmission dysfunction contribute to the pathophysiology of several neuropsychiatric disorders, which include depression, schizophrenia and drug abuse (Fibiger, H.C., et al., "In Depression and Mania: from neurobiology to treatment" *Raven Press,* New York **1995**, pp. 1-17; Roth, B.L., et al., *J. Pharmacol. Exp. Ther.* **1992**, 260, pp. 1361-1365; Koob, G.F, et al., *Trends Pharmacol. Sci.* **1992**, 13, pp. 177-184; Brown, A.S. , et al., *J. Neural. Trans.* **1993,** 91, pp. 75-109). Esposito, E., et al., "Serotonin-Dopamine Interaction as focus of Novel Antidepressant Drugs" *Curr. Drug Targets* **2006**, 7, pp177-185, suggests that drugs acting on the 5-HT system (e.g. SSRI's and 5-HT_{2C} receptor antagonist) exert their antidepressant action by enhancing dopaminergic transmission in the mesolimbic system, and the use of such drugs, which influence the mesolimbic DA transmission might be important and useful in the search of new antidepressants for the treatment of depression.

Furthermore, Axford L. et al. describe the development of triple 5-HT, NE and DA re-uptake inhibitors for treatment of depression. (2003, *Bioorganic & Medical Chemistry Letters*, 13, 3277-3280: "Bicyclo[2.2.1.]heptanes as novel triple re-uptake inhibitors for the treatment of depression"). Wellbutrin (bupropion) which has DA re-uptake activity in vitro and in vivo, show antidepressant efficacy. Other combination studies have indicated that addition of some affininity at the DA uptake site may have some clinical benefit (Nelson, J. C. J. *Clin.*

Psychiatry **1998**, 59, 65; Masand, P. S. et al. *Depression Anxiety* **1998**, 7, 89; Bodkin, J. A et al. *J. Clin. Psychiatry* **1997**, 58, 137).

The combination of an SSRI and a norepinephrine and dopamine reuptake inhibitor, has been shown to have better efficacy in SSRI-non-responders (Lam R. W. *et al.* "Citalopram and Bupropion-SR: Combining Versus Switching in Patients With Treatment-Resistant Depression." *J. Clin. Psychiatry* **2004**, *65*, 337-340).

There is clinical evidence suggesting that the combination of an SSRI and a norepinephrine and dopamine reuptake inhibitor induces less sexual dysfunction, than treatment with SSRI's alone (Kennedy S. H. *et al.* " Combining Bupropion SR With Venlafaxine, Paroxetine, or Duloxetine: A Preliminary Report on Pharmacokinetic, Therapeutic, and Sexual Dysfunction Effects" *J. Clin. Psychiatry* **2002,** *63*, 181-186).

The development of triple serotonin, norepinephrine and dopamine re-uptake inhibitors are currently the focus of many pharmaceutical companies, for their improved efficacy and reduced delay of action (Millan, M. J., et al. "Multi-target strategies for the improvement of depressive states: Conceptual Foundations And Neuronal Substrates, Drug Discovery And Therapeutic Application." *Pharmacology & Therapeutics.* 110 (2006), 135-370).

The present invention provides novel indane compounds which are inhibitors of serotonin, norepinephrine and dopamine re-uptake. The compounds of the invention are therefore useful in the treatment of affective disorders, pain disorders, attention deficit hyperactivity disorder (ADHD), substance abuse, cognitive deficits and stress urinary incontinence.

SUMMARY OF THE INVENTION

An object of the invention is to provide compounds of the Formulas I-X, as defined below, which are inhibitors of serotonin, norepinephrine and dopamine re-uptake. The compounds of the invention are therefore useful in the treatment of affective disorders, pain disorders,

attention deficit hyperactivity disorder (ADHD), cognitive disorders, substance abuse, smoking cessation and stress urinary incontinence.

In one embodiment, the compounds of the Formulas I-X, as defined below, are useful in the treatment of affective disorders. To further illustrate but without limiting the invention, the affective disorder to be treated is selected from the group consisting of depressive disorders and anxiety disorders.

In one embodiment, the depressive disorders to be treated are selected from the group consisting of major depressive disorder, melancholia, postnatal depression, dysthymia and depression associated with bipolar disorder, Alzheimer's, psychosis or Parkinson's disease. To further illustrate without limiting the invention, an embodiment of the invention concerns the treatment of depression associated with bipolar disorder; another embodiment concerns the treatment of depression associated with Alzheimer's; another embodiment concerns the treatment of depression associated with psychosis; and another embodiment concerns the treatment of depression associated with Parkinson's disease.

In another embodiment, the anxiety disorders to be treated are selected from the group consisting of general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

In another embodiment, the compounds of the invention are useful in the treatment of pain disorders. To further illustrate but without limiting the invention, the pain disorder to be treated is selected from the group consisting of fibromyaglia syndrome (FMS), overall pain, back pain, shoulder pain, headache as well as pain while awake and during daily activities. To further illustrate without limiting the invention, an embodiment of the invention concerns the treatment of fibromyalgia syndrome (FMS); another embodiment concerns the treatment of overall pain; another embodiment concerns the treatment of back pain; another embodiment concerns the treatment of shoulder pain; another embodiment concerns the treatment of headache; and another embodiment concerns the treatment of pain while awake and during daily activities.

In another embodiment, the compounds of the invention are useful in the treatment of attention deficit hyperactivity disorder (ADHD) and other cognitive disorders.

In another embodiment, the compounds of the invention are useful in the treatment of both substance abuse and smoking cessation.

In another embodiment, the compounds of the invention are useful in the treatment of stress urinary incontinence.

In a second aspect, the present invention relates to the use of a compound of the Formulas I-X, as defined below, for the manufacture of a medicament useful for the treatment of affective disorders, pain disorders, attention deficit hyperactivity disorder (ADHD), cognitive disorders, substance abuse, smoking cessation and stress urinary incontinence.

In one embodiment, the present invention relates to the use of a compound of the Formulas I-X, as defined below, for the manufacture of a medicament useful for the treatment of affective disorders. To further illustrate without limiting the invention, the affective disorder to be treated is selected from the group consisting of depressive disorders and anxiety disorders.

In one embodiment, the depressive disorders to be treated are selected from the group consisting of major depressive disorder, melancholia, postnatal depression, dysthymia and depression associated with bipolar disorder, Alzheimer's, psychosis or Parkinson's disease. To further illustrate without limiting the invention, an embodiment of the invention concerns the treatment of depression associated with bipolar disorder; another embodiment concerns the treatment of depression associated with Alzheimer's; another embodiment concerns the treatment of depression associated with psychosis; and another embodiment concerns the treatment of depression associated with Parkinson's disease.

In another embodiment, the anxiety disorders to be treated are selected from the group consisting of general anxiety disorder, social anxiety disorder, post traumatic stress disorder,

obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

In another embodiment, the invention relates to the use of a compound of Formulas I-X, as defined below, for the manufacture of a medicament useful for the treatment of pain disorders. To further illustrate without limiting the invention, the pain disorder to be treated is selected from the group consisting of fibromyaglia syndrome (FMS), overall pain, back pain, shoulder pain, headache as well as pain while awake and during daily activities.

In another embodiment, the invention relates to the use of a compound of Formulas I-X, as defined below, for the manufacture of a medicament useful for the treatment of attention deficit hyperactivity disorder (ADHD) and other cognitive disorders.

In another embodiment, the invention relates to the use of a compound of Formulas I-X, as defined below, for the manufacture of a medicament useful for the treatment of substance abuse and smoking cessation.

In another embodiment, the invention relates to the use of a compound of Formulas I-X, as defined below, for the manufacture of a medicament useful for the treatment of stress urinary incontinence.

In a third aspect, the present invention relates to a pharmaceutical composition comprising a compound of Formulas I-X, as defined below, in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

In a fourth aspect, the present invention relates to treating a disease, where the inhibition of serotonin, and/or norepinephrine and/or dopamine re-uptake is implicated, comprising administration of a therapeutically effective amount of a compound of the Formulas I-X, as defined below, to a mammal including humans.

In a fifth aspect, the present invention relates to a method of treating affective disorders, pain disorders, attention deficit hyperactivity disorder (ADHD), cognitive disorders, substance

abuse, smoking cessation and stress urinary incontinence, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans.

In one embodiment, the present invention relates to a method of treating affective disorders, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans. To further illustrate without limiting the invention, the affective disorder to be treated is selected from the group consisting of depressive disorders and anxiety disorders.

In one embodiment, the depressive disorders to be treated are selected from the group consisting of major depressive disorder, melancholia, postnatal depression, dysthymia and depression associated with bipolar disorder, Alzheimer's, psychosis or Parkinson's disease. To further illustrate without limiting the invention, an embodiment of the invention concerns the treatment of depression associated with bipolar disorder; another embodiment concerns the treatment of depression associated with Alzheimer's; another embodiment concerns the treatment of depression associated with psychosis; and another embodiment concerns the treatment of depression associated with Parkinson's disease.

In another embodiment, the anxiety disorders to be treated are selected from the group consisting of general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

In further embodiment, the depressive disorder to be treated is selected from the group consisting of major depressive disorder, melancholia, postnatal depression, dysthymia and depression associated with bipolar disorder, Alzheimer's, psychosis or Parkinson's disease. To further illustrate without limiting the invention, an embodiment of the invention concerns the treatment of depression associated with bipolar disorder; another embodiment concerns the treatment of depression associated with Alzheimer's; another embodiment concerns the treatment of depression associated with psychosis; another embodiment concerns the treatment of depression associated with Parkinson's disease.

In even a further embodiment, the present invention relates to a method of treating anxiety disorders, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans.

In further embodiment, the anxiety disorders to be treated are selected from the group consisting of general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

In another embodiment, the present invention relates to a method of treating pain disorders, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans. To further illustrate without limiting the invention, the pain disorder to be treated is selected from the group consisting of fibromyaglia syndrome (FMS), overall pain, back pain, shoulder pain, headache as well as pain while awake and during daily activities.

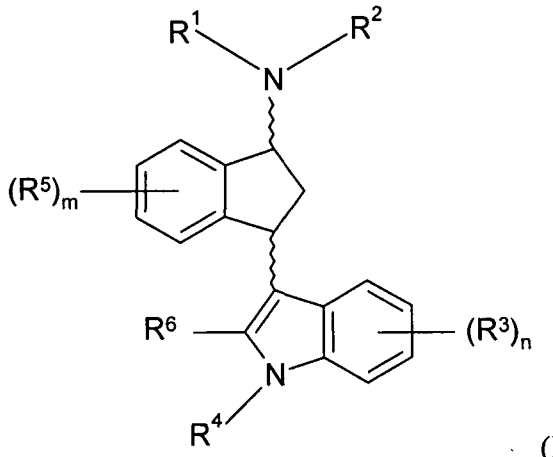
In another embodiment, the present invention relates to a method of treating attention deficit hyperactivity disorder (ADHD) and other cognitive disorders, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans.

In another embodiment, the present invention relates to a method of treating substance abuse and smoking cessation, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans.

In another embodiment, the present invention relates to a method of treating stress urinary incontinence, comprising the administration of a therapeutically effective amount of a compound of the Formula I-X, as defined below, to a mammal including humans.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides compounds that are represented by the Formula I



(I)

Wherein each R^1 and R^2 are independently hydrogen, C_1-C_8-straight or branched alkyl or C_3-C_8-cycloalkyl; or wherein R^1 and R^2 and the nitrogen to which they are attached form azetidine, piperidine, pyrrolidine, azapane or morpholine;

Wherein each R^3 is independently hydrogen, C_1-C_8-straight or branched alkyl, C_1-C_5-alkoxy, C_1-C_8-straight or branched polyfluoroalkyl, halogen, cyano, hydroxyl, tetrazole- optionally substituted with methyl, or amino; or wherein two R^3 groups on adjacent carbons combine together to form a methylenedioxy linker;

wherein R^4 is hydrogen, C_1-C_8-straight or branched alkyl or C_3-C_8-cycloalkyl;

wherein each R^5 is hydrogen, halogen, C_1-C_5-alkoxy, C_1-C_8-straight or branched alkyl, C_1-C_8-straight or branched polyfluoroalkyl, cyano, or hydroxyl;

m is an integer from 1 to 4 inclusive;

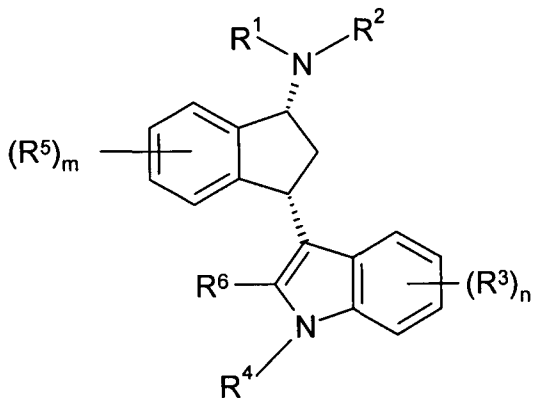
n is an integer from 1 to 4 inclusive; and

wherein R^6 is hydrogen, C_1-C_8-straight or branched alkyl or phenyl;
or pharmaceutically acceptable salts thereof.

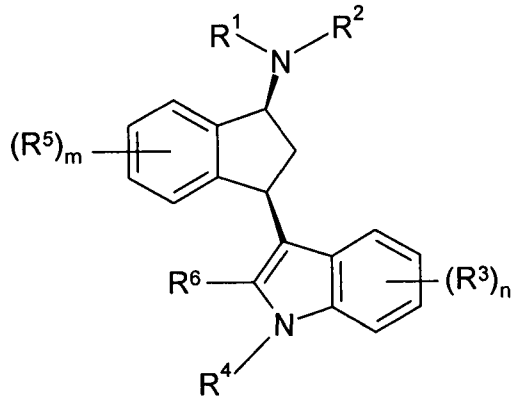
In one embodiment the compounds represented by the Formula I are the pure enantiomers, diasteromers and mixtures thereof.

In another embodiment the compound represented by the Formula I is the cis isomer of Formula II and III; In another embodiment the compound represented by the Formula I is the trans isomer of Formula IV and V.

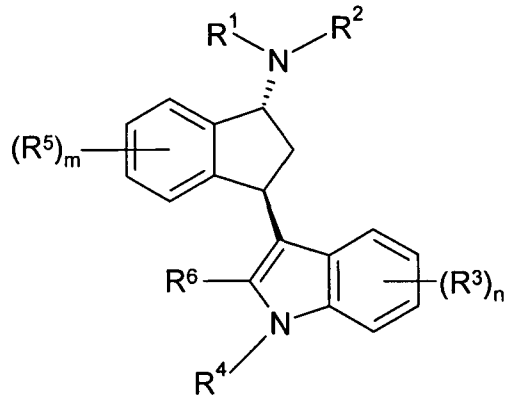
In another embodiment, the present invention relates to compounds of the Formula II-V



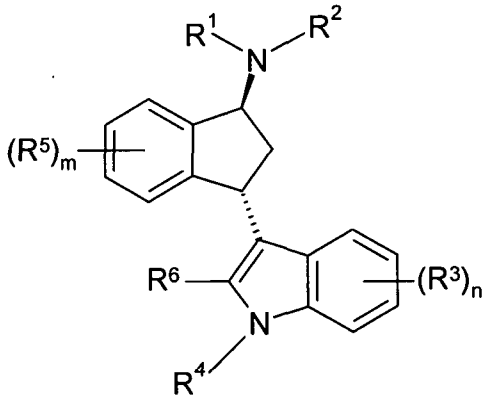
(II);



(III);



(IV); and



(V);

Wherein R^1, R^2, R^3, R^4, R^5, R^6, m and n are as defined above.

In one embodiment R^1 is hydrogen. In one embodiment R^2 is methyl. In one embodiment R^4 is hydrogen. In one embodiment R^3 is selected form the group consisting of hydrogen, halogen, and methoxy. In one embodiment R^3 is a hydrogen or halogen. In one embodiment the halogen is fluorine or chlorine. In one embodiment R^5 and R^6 are hydrogen.

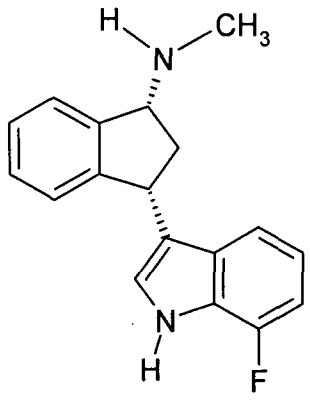
In another embodiment R^1 is hydrogen and R^2, R^3, R^4, R^5, and R^6 are as defined above in Formulas II-V. In a further embodiment R^1 is hydrogen, R^2 is methyl, R^3, R^4, R^5 and R^6 are as defined above in Formulas II-V.

In a further embodiment, R^1 is hydrogen, R^2 is methyl, R^4 is hydrogen, and R^3, R^5 and R^6 are as defined above in Formulas II-V.

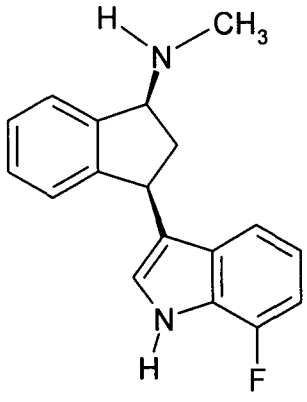
In a further embodiment, R^1 is hydrogen, R^2 is methyl, R^4 is hydrogen, R^3 is hydrogen, halogen or methoxy, and the halogen is selected from the group consisting of fluoro or chloro, and R^5 and R^6 are as defined above in Formulas II-V.

In a further embodiment, R^1 is hydrogen, R^2 is methyl, R^4 is hydrogen, R^3 is hydrogen, halogen or methoxy, and the halogen is selected from the group consisting of fluoro or chloro, and R^5 and R^6 are hydrogen.

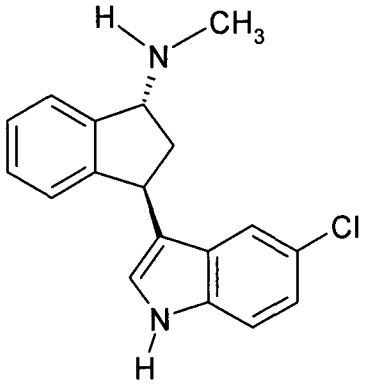
In a further embodiment, the present invention relates to compounds of the Formula VI-X



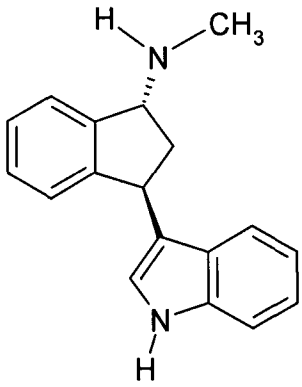
(VI);



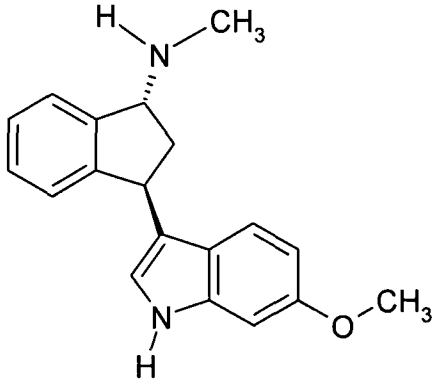
(VII);



(VIII);



(IX); and



(X)

or a pharmaceutically acceptable salt thereof.

As used herein, it is understood that compounds of Formula I-X are meant to include all the examples exemplified herein.

In the present invention the term Halogen means fluoro, chloro, bromo or iodo.

In the present invention, the term "C_1-C_8 straight or branched alkyl" refers to a saturated hydrocarbon having from one to eight carbon atoms inclusive. Examples of such substituents include, but are not limited to, methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2-methyl-1-propyl, n-pentyl and n-octyl.

Furthermore, the term "C_3-C_8 cycloalkyl" refers to a saturated cyclohydrocarbon ring having from three to eight carbon atoms inclusive. Included within this term are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexyl and cyclooctyl.

The term "C_1-C_5-alkoxy" refers to a saturated alkoxy group having from one to five carbon atoms inclusive with the open valency on the oxygen. Examples of such substituents include, but are not limited to, methoxy, ethoxy, n-butoxy, t-butoxy and n-pentyloxy.

The term "C_1-C_8 straight or branched polyfluoroalkyl" refers to a saturated hydrocarbon having from one to eight carbon atoms inclusive substituted with one or more fluorine atoms. Examples of such substituents include, but are not limited to, trifluoromethyl, pentafluoroethyl, 1-fluoroethyl and 1,2-difluoroethyl and 2,3-difluorooctyl.

A "therapeutically effective amount" of a compound as used herein means an amount sufficient to cure, alleviate or partially arrest the clinical manifestations of a given disease and/or its complications. An amount adequate to accomplish this is defined herein as "therapeutically effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician.

The term "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the

patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. Nonetheless, prophylactic (preventive) and therapeutic (curative) treatment are two separate aspect of the invention. The patient to be treated, i.e. the patient in need thereof, may be a mammal, in particular a human being.

The salts of the invention are may be acid addition salts. The acid addition salts of the invention are may be pharmaceutically acceptable salts of the compounds of the invention formed with non-toxic acids. Acid addition salts include salts of inorganic acids as well as organic acids. Examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in *J. Pharm. Sci.* **1977**, *66*, 2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified and any mixtures thereof including racemic and diastereomeric mixtures, i.e. a mixture of stereoisomers, are included within the scope of the invention.

Racemic forms can be resolved into the optical antipodes by known methods, for example, by fractional separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives. Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981). Optically active compounds can also be prepared from optically active starting materials, by stereoselective synthesis or by enzymatic resolution.

The pharmaceutical compositions of this invention, or those which are manufactured in accordance with this invention, may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used. Tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, such as sterile water, adjusting the solution to desired volume, sterilizing the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Conveniently, the compounds of the invention may be formulated in a unit dosage form, each dosage containing from about 0.01 to about 1000 mg, or from about 0.05 to about 5000, or from about 0.1 to about 1000 mg, the actual dosage may however vary e.g. according to the specific compound. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art.

The compounds of the invention are effective over a wide dosage range. For example, dosages per day normally fall within the range of about 0.01 to about 100 mg/kg of body weight, or within the range of about 0.1 to about 75 mg/kg. However, it will be understood that the amount of the compound actually administered will be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, and the severity of the patient's symptoms, and therefore the above dosage ranges are not intended to limit the scope of the invention in any way. In some instances dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several smaller doses for administration throughout the day.

All references cited throughout the specification are hereby incorporated by reference in their entirety.

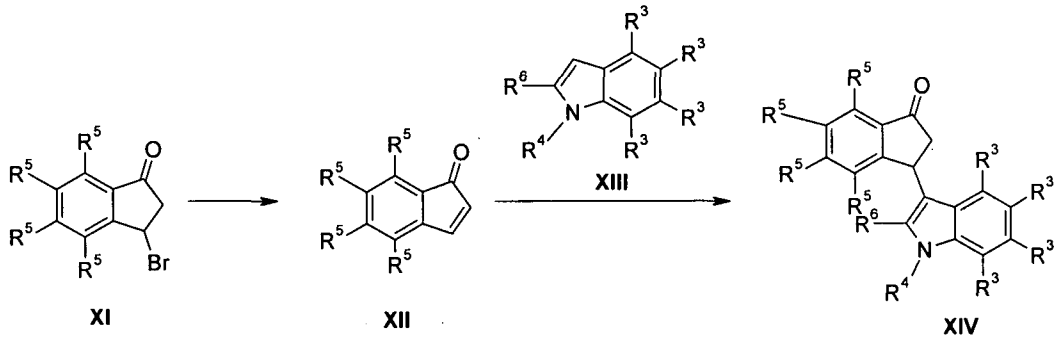
General methods of preparation of intermediates for the synthesis of compounds of the invention

7-Fluoroindole was synthesized according to: Bartoli, Guiseppe; Palmieri, Gianni; Bosco, Marcella; Dalpozzo, Renato; Tetrahedron Lett., 30, 16, 1989, 2129-2132.

Indole, 5-Chloroindole and 6-methoxyindole were purchased from Aldrich.

Method 1: 3-(1H-Indol-3-yl)-indan-1-ones

3-(1H-Indol-3-yl)-indan-1-ones can be prepared as shown in Scheme 1.

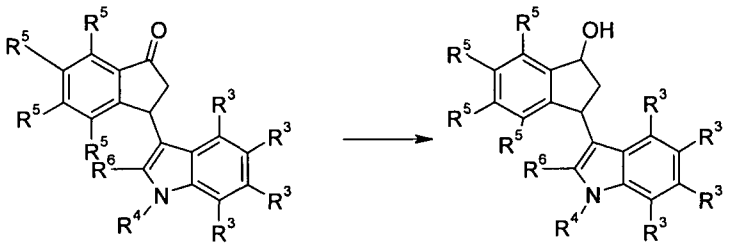


Scheme 1. R^3, R^4, R^5 and R^6 are as defined above.

3-Bromo-indan-1-ones of general Formula XI are treated with a base such as triethylamine to form inden-1-ones of general Formula XII. Treatment of inden-1-ones of general Formula XII with indoles of general Formula XIII in the presence of a Lewis acid catalyst such as scandium triflate or copper triflate give 3-(1H-indol-3-yl)-indan-1-ones of general Formula XIV.

Method 2: *cis*-3-(1H-Indol-3-yl)-indan-1-ols

cis-3-(1H-Indol-3-yl)-indan-1-ols of general Formula XV are prepared as shown in Scheme 2.



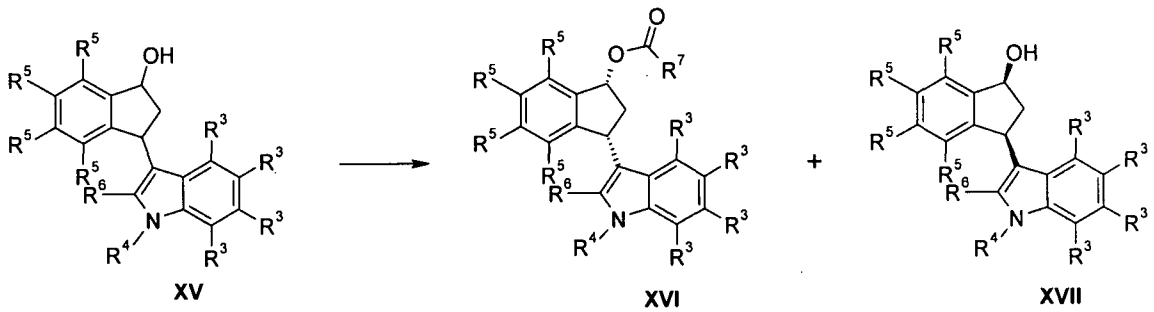
XIV XV

Scheme 2. R^3-R^6 are as defined above.

3-(1H-Indol-3-yl)-indan-1-ones of general Formula XIV are treated with a reducing agent such as sodium borohydride to give *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formula XV.

Method 3: Enzymatic chiral resolution of *cis*-3-(1H-indol-3-yl)-indan-1-ols

cis-3-(1H-Indol-3-yl)-indan-1-ols of general Formula XV are resolved into their enantiomers as shown in Scheme 3.



XV XVI XVII

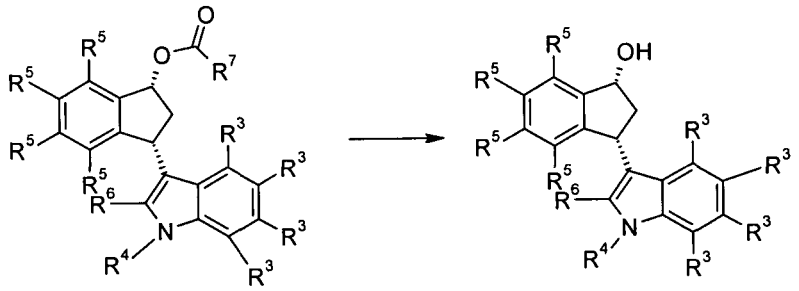
Scheme 3. R^3-R^6 are as defined above, and R^7 is a C_1-C_8 straight or branched alkyl group.

cis-3-(1H-Indol-3-yl)-indan-1-ols of general Formula XV are resolved into their enantiomers by treatment of racemic *cis*-3-(1H-indol-3-yl)-indan-1-ols with an irreversible acyl donor

such as vinyl butyrate in the presence of a lipase such as Novozym 435 (Availabale from Novozymes A/S, Krogshoejvej 36, 2880 Bagsvaerd, Denmark). One enantiomer is then esterificated to form ester of general Formula XVI while the other enantiomer of general Formula XVII is left unreacted. The compounds of general Formulae XVI and XVII are separated by standard chromatographic techniques.

Method 4: Optically active *cis*-3-(1H-indol-3-yl)-indan-1-ols

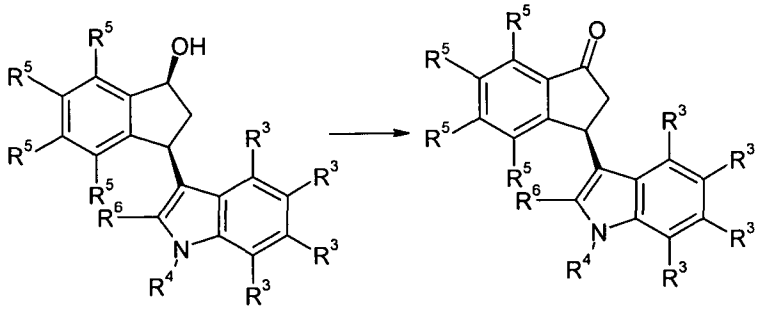
Optically active *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formula XVIII are obtained by hydrolysis of esters of general Formula XVI or by treatment of esters of general formula XVI with a transesterification reagent such as sodium methoxide in methanol as shown in Scheme 4.



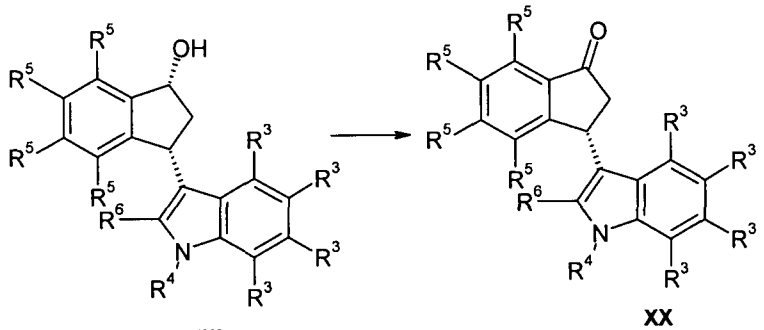
Scheme 4. R^3-R^6 are as defined above, and R^7 is a C_1-C_8 straight or branched alkyl group.

Method 5: Optically active 3-(1H-indol-3-yl)-indan-1-ones

Optically active *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XVII and XVIII are oxidized by an oxidant such as the Dess-Martin periodane to give optically active 3-(1H-indol-3-yl)-indan-1-ones general Formulae XIX and XX as shown in Scheme 5.



XVII XIX

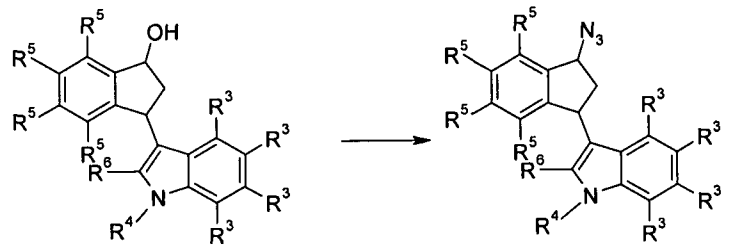


XVIII XX

Scheme 5. R^3-R^6 are as defined above.

Method 6: *trans*-3-(3-Azido-indan-1-yl)-1H-indoles

trans-3-(3-Azido-indan-1-yl)-1H-indoles of general Formula XXI are prepared as shown in Scheme 6.



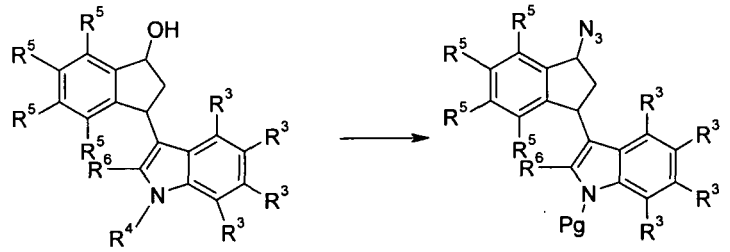
XV (or XVII or XVIII) XXI

Scheme 6. R^3-$R^6$are as defined above.

Treatment of racemic *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XV or treatment of optically active *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XVII or XVIII with an azidating reagent such as diphenyl phosphoryl azide and a base such as DBU provides racemic or optically active *trans*-3-(3-azido-indan-1-yl)-1H-indoles of general Formula XXI, respectively.

Method 7: *trans*-[3-(3-Azido-indan-1-yl)-indol-1-yl]-phosphonic acid diphenyl esters

trans-[3-(3-Azido-indan-1-yl)-indol-1-yl]-phosphonic acid diphenyl esters of general Formula XXII are prepared as shown in Scheme 7.

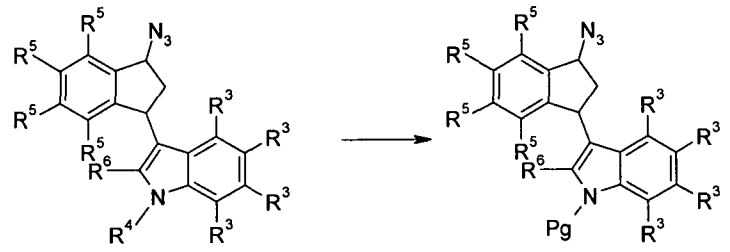


Scheme 7. R^3-R^6 are as defined above, and Pg is an indole protecting group such as a diphenyl phosphoryl group.

Treatment of racemic *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XV with R^4 = H or treatment of optically active *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XVII or XVIII with R^4 = H with an excess of diphenyl phosphoryl azide and a base such as DBU provides racemic or optically active *trans*-[3-(3-azido-indan-1-yl)-indol-1-yl]-phosphonic acid diphenyl esters of general formula XXII, respectively.

Method 8: *N*-protected *trans*-3-(3-azido-indan-1-yl)-1H-indoles

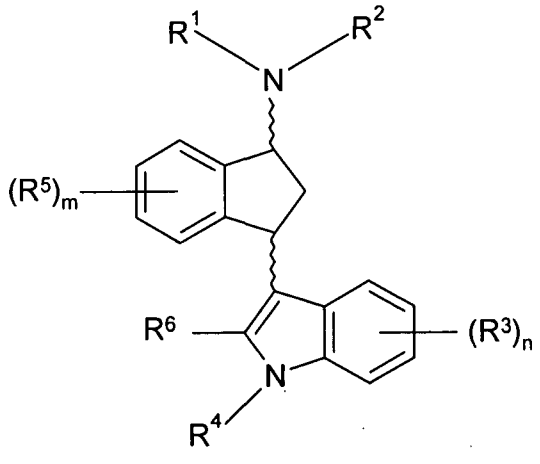
N-protected *trans*-3-(3-azido-indan-1-yl)-1H-indoles of general Formula XXII are prepared by the treatment of *trans*-3-(3-azido-indan-1-yl)-1H-indoles of general Formula XXI with R^4 = H with an appropriate protection group reagent such as *p*-tolouensulfonic acid chloride as shown in Scheme 8.



XXI (R^4 = H) XXII

Scheme 8. R^3-R^6 are as defined above, and Pg is an indole protecting group such as a tosyl group.

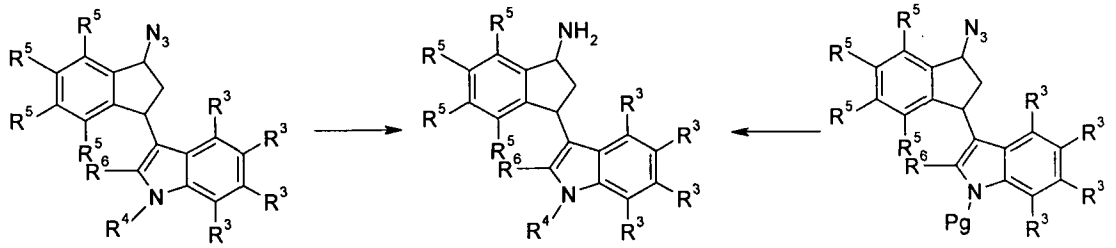
General methods of preparation of the compounds of the invention



(I)

Method 9: *trans*-3-(1H-Indol-3-yl)-indan-1-ylamines

Racemic or optically active *trans*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXIII are prepared by the reduction of racemic or optically active *trans*-3-(3-azido-indan-1-yl)-1H-indoles of general Formula XXI or racemic or optically active *N*-protected *trans*-3-(3-azido-indan-1-yl)-1H-indoles of general Formula XXII under appropriate reducing conditions such as addition of sodium borohydride, in the presence of an appropriate transition metal catalyst such as Pd/C under hydrogen or treatment with a trimethyl phosphine in pyridine and aqueous ammonium hydroxide as shown in Scheme 9, respectively.

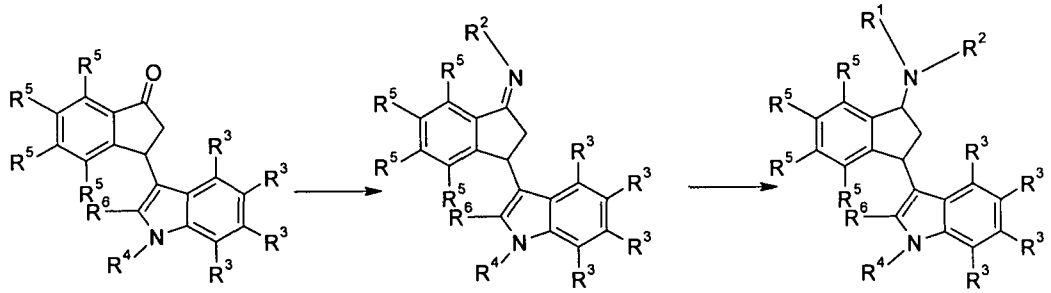


XXI XXIII XXII

Scheme 9. R^3-R^6 are as defined above, and Pg is an indole protecting group such as a diphenyl phosphoryl group.

Method 10: *cis*-3-(1H-Indol-3-yl)-indan-1-ylamines

Racemic or optically active *cis*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV with R^1 = H are prepared as shown in Scheme 10.



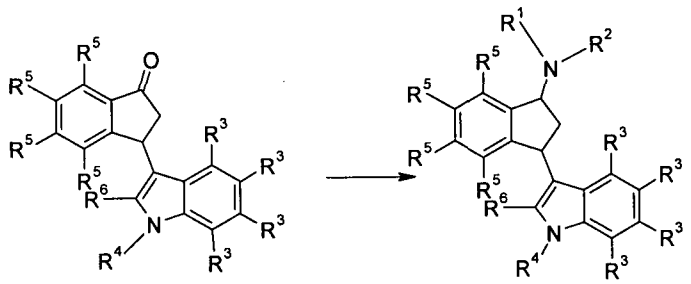
XIV (or XIX or XX) XXIV XXV

Scheme 10. R^1 = H and R^2, R^3–R^6 are as defined above.

Racemic or optically active 3-(1H-indol-3-yl)-indan-1-ones of general Formula XIV, XIX or XX are treated with an amine (NH_2R^2) and a drying reagent such as tetraethoxy silane to give imines of Formula XXIV, which are reduced using a reducing agent such as sodium borohydride or by treatment with hydrogen in the presence of transition metal catalyst such as PtO_2 to give racemic or optically active *cis*-3-(1H-Indol-3-yl)-indan-1-ylamines of general Formula XXV with R^1=H.

Method 11: *cis*-3-(1H-Indol-3-yl)-indan-1-ylamines

Racemic or optically active *cis*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV are prepared as shown in Scheme 11.

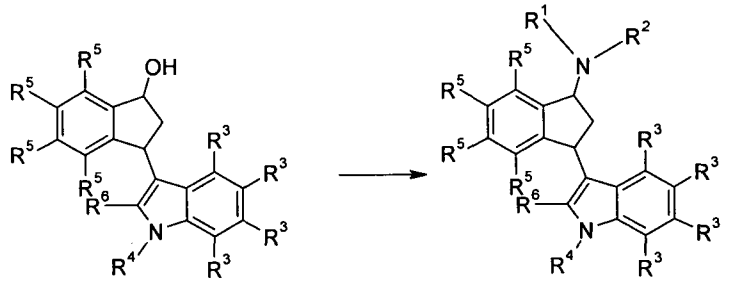


XIV (or **XIX** or **XX**) **XXV**

Scheme 11. R^1-R^6 are as defined above.

A 3-(1H-Indol-3-yl)-indan-1-one of general Formula XIV, XIX or XX are treated with an amine (NHR^1R^2) and a reducing reagent such as sodium cyanoborohydride in an acetic acid/methanol solution of appropriate pH to give racemic or optically active *cis*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV, respectively.

Method 12: *cis*-3-(1H-Indol-3-yl)-indan-1-ylamines and *trans*-3-(1H-Indol-3-yl)-indan-1-ylamines



XV
(or XVII or XVIII)

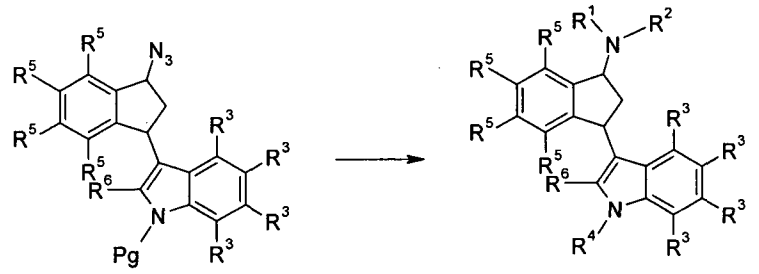
XXV

Scheme 12. R^1-R^6 are as defined above.

Treatment of racemic *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XV or treatment of optically active *cis*-3-(1H-indol-3-yl)-indan-1-ols of general Formulae XVII or XVIII with an alcohol-activating reagent and a base such as triethyl amine followed reaction with an amine (NHR^1R^2) provides a mixture of racemic or optically active *cis*- and *trans*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV, which are separated by standard chromatographic methods such as HPLC or flash chromatography to give racemic or optically active *cis*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV or racemic or optically active *trans*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV as shown in Scheme 12.

Method 13: *trans*-3-(1H-Indol-3-yl)-indan-1-ylamines

trans-3-(1H-Indol-3-yl)-indan-1-ylamines of general Formula XXVI with R^1, R^4 = H are prepared by the treatment of *N*-protected *trans*-3-(3-azido-indan-1-yl)-1H-indoles of general Formula XXII with $(R^1)_2BBr$ followed by removal of the indole protection group as shown in Scheme 13.

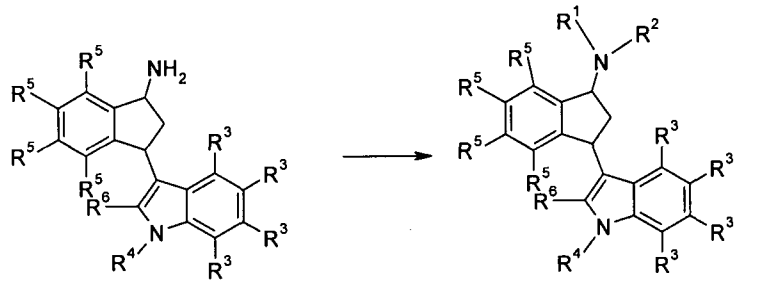


XXII XXVI (R^1,R^4 = H)

Scheme 13. R^2, R^3, R^5 and R^6 are as defined above, and Pg is an indole protection group such as a tosyl group or a diphenyl phosphoryl group.

Method 14: *trans*-3-(1H-Indol-3-yl)-indan-1-ylamines

trans-3-(1H-Indol-3-yl)-indan-1-ylamines of general Formula XXVI with R^1, R^4 = H are prepared by the treatment of *trans*-3-(1H-Indol-3-yl)-indan-1-ylamines of general Formula XXIII with R^4 = H with methyl chloroformate followed by reduction with an appropriate reducing reagent such as lithium aluminum hydride as shown in Scheme 14.



XXIII (R^4 = H) XXVI (R^1,R^4 = H; R^2=Me)

Scheme 14.R^3, R^5 and R^6 are as defined above.

Method 15: Optically active 3-(1H-Indol-3-yl)-indan-1-ylamines

Racemic *cis*- or *trans*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV and XXVI are separated into their pairs of optically active *cis*- or *trans*-3-(1H-indol-3-yl)-indan-

1-ylamines, respectively, by chromatographic techniques such as chiral supercritical fluid chromatography (SFC) and chiral HPLC.

Method 16: Optically active 3-(1H-Indoly-3-yl)indan-1-ylamines

Racemic *cis- or trans*-3-(1H-indol-3-yl)-indan-1-ylamines of general Formula XXV and XXVI are separated into their pairs of optically active *cis-* or *trans*-3-(1H-indol-3-yl)-indan-1-ylamines, respectively, by fractional separation of diastomeric salts with an optically active acid and liberated the optically active amine compound by treatment with a base.

EXPERIMENTAL SECTION

LC-MS Methods A and B, general: Solvent system: A = water/TFA (100:0.05) and B = water/acetonitrile/TFA (5:95:0.035) (TFA = trifluoroacetic acid). Purity was determined by integration of the UV (254 nm) and ELSD trace and retention times (RT) are expressed in minutes. MS instruments are from PESciex (API), equipped with APPI-source and operated in positive ion mode.

Method A: API 150EX and Shimadzu LC8/SLC-10A LC system. Column: 30 x 4.6 mm Waters Symmetry C18 with 3.5 µM particles operated at room temperature. Linear Gradient elution with 90% A to 100% B in 4 min and a flow rate of 2 ml/min.

Method B: API 150EX and Shimadzu LC8/SLC-10A LC system. Column: 30 x 4.6 mm Waters Symmetry C18 with 3.5 µM particles operated at 40°C. Linear Gradient elution with 90% A to 100% B in 2.4 min and a flow rate of 3.3 ml/min.

LC-MS TOF (TOF = time of flight) Method C: micromass LCT 4-ways MUX equipped with a Waters 2488/Sedex 754 detector system. Column: 30 X 4.6 mm Waters Symmetry C18 column with 3.5 µm particle size operated at room temperature. Linear Gradient elution with

90% A to 100% B in 4 min and a flow rate of 2 ml/min. Purity was determined by integration of the UV (254 nm) and ELSD trace and retention times (RT) are expressed in minutes.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX 500 at 500.13 MHz and 125.67, respectively. Deuterated chloroform (99.8% D) or dimethylsulfoxide (99.9% D) were used as solvents. TMS was used as internal reference standard. Chemical shifts are expressed as ppm values. The following abbreviations are used for multiplicity of NMR signals: s=singlet, d=doublet, t=triplet, q=quartet, qv=quintet, h=heptet, dd=double doublet, dt=double triplet, dq=double quartet, tt=triplet of triplets, m= multiplet, b=broad.

EXAMPLES

Synthesis of 3-bromo-indan-1-one

390g (2.2mol) *N*-bromosuccinimde (powder with no lumps) and 0.5g benzoyl peroxide were added to 264g indan-1-one in 1500 mL CCl_4 and refluxed with mechanical stirring for 1.5 hours. The colour of the reaction mixture suddenly changed to yellow and all *N*-bromosuccinimde (heavier than CCl_4) was converted to succinimide (lighter than CCl_4). The reaction mixture was cooled to 20°C, filtered and concentrated *in vacuo*. Crude 3-bromo-indan-1-one was dissolved in 600mL ethyl acetate/heptane (1:2), cooled 2 hours on an ice bath and then left in a freezer over night to give 257g crystals of 3-bromo-indan-1-one (62% yield).

Synthesis of 3-(7-fluoro-1H-indol-3-yl)-indan-1-one (Method 1)

Triethylamine (4.5 mL; 32 mmol; 1.2 equiv.) was added to 3-bromo-indan-1-one (5.6 g; 27 mmol) in 100 mL THF at 0°C and stirred 1h at r.t. The reaction mixture was filtered to remove triethylammonium bromide and concentrated *in vacuo* to give inden-1-one.

7-Fluoroindole (3.3g, 22mmol) and $Sc(OTf)_3$ (550mg, 5mol%) were added to inden-1-one in 100 mL CH_2Cl_2 at 0°C. The reaction mixture was allowed to warm to room temperature over night. 100mL ethyl acetate was added and the mixture was filtered through a silica gel plug and concentrated *in vacuo*. After flash chromatography (heptane/ethyl acetate, silica gel) 5.9g 3-(7-fluoro-1H-indol-3-yl)-indan-1-one (82%) was isolated.

The following compounds were synthesized in a similar way:

3-(1H-indol-3-yl)-indan-1-one
3-(1-Methyl-1H-indol-3-yl)-indan-1-one
3-(5-Fluoro-1H-indol-3-yl)-indan-1-one
3-(6-Fluoro-1H-indol-3-yl)-indan-1-one
3-(6-Methoxy-1H-indol-3-yl)-indan-1-one
3-(5-Fluoro-2-methyl-1H-indol-3-yl)-indan-1-one
3-(4-Chloro-1H-indol-3-yl)-indan-1-one
3-(5-Chloro-1H-indol-3-yl)-indan-1-one
3-(7-Chloro-1H-indol-3-yl)-indan-1-one
5-Fluoro-3-(7-methyl-1H-indol-3-yl)-indan-1-one
3-(6-Bromo-1H-indol-3-yl)-5-fluoro-indan-1-one
3-(4-Chloro-1H-indol-3-yl)-6-fluoro-indan-1-one
3-(4,6-Difluoro-1H-indol-3-yl)-6-fluoro-indan-1-one
3-(4-Chloro-1H-indol-3-yl)-6-methoxy-indan-1-one
3-(5,6-Difluoro-1H-indol-3-yl)-6-methoxy-indan-1-one
5-Chloro-3-(5-fluoro-1H-indol-3-yl)-indan-1-one
3-(6-Chloro-3-oxo-indan-1-yl)-1H-indole-5-carbonitrile
6-Chloro-3-(5-methoxy-1H-indol-3-yl)-indan-1-one
6-Chloro-3-(7-methoxy-1H-indol-3-yl)-indan-1-one

Synthesis of *cis*-3-(1H-indol-3-yl)-indan-1-ol (Method 2)

$NaBH_4$ (6.2g, 163mmol, 2 equiv.) was added to 3-(1H-indol-3-yl)-indan-1-one (20g, 80.9mmol) in 200mL methanol and 100mL THF at 0°C. The reaction mixture was allowed to warm to room temperature over night. Aqueous work up gave racemic *cis*-3-indolyl-indan-1-ol (quantitative).

The following compounds were synthesized in a similar way:

cis-3-(6-Fluoro-1H-indol-3-yl)-indan-1-ol
cis-3-(6-Methoxy-1H-indol-3-yl)-indan-1-ol
cis-3-(5-Chloro-1H-indol-3-yl)-indan-1-ol
cis-3-(4-Chloro-1H-indol-3-yl)-6-fluoro-indan-1-ol
cis-6-Chloro-3-(5-methoxy-1H-indol-3-yl)-indan-1-ol

Synthesis of butyric acid (1*R*,3*S*)-3-(1H-indol-3-yl)-indan-1-yl ester and (1*S*,3*R*)-3-(1H-indol-3-yl)-indan-1-ol (Method 3)

Novozym 435 (1g) (Available from Novozymes A/S, Krogshoejvej 36, 2880 Bagsvaerd, Denmark) and vinyl butyrate (20.5 mL, 162mmol) were added to racemic *cis*-3-indolyl-indan-1-ol (80.9mmol) in 200mL toluene. The reaction mixture was shaken for 2 days under argon until ^{1}H –NMR shows 50% conversion. The reaction mixture was filtered and concentrated *in vacuo*. After flash chromatography (heptane/ethyl acetate, silica gel) 13.49g butyric acid (1*R*,3*S*)-3-(1H-indol-3-yl)-indan-1-yl ester and 9.78g (1*S*,3*R*)-3-(1H-indol-3-yl)-indan-1-ol were isolated.

The following compounds were synthesized in a similar way:

Butyric acid (1*R*,3*S*)-3-(7-fluoro-1H-indol-3-yl)-indan-1-yl ester
(1*S*,3*R*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-ol
(1*S*,3*R*)-3-(5-Chloro-1H-indol-3-yl)-indan-1-ol
(1*S*,3*R*)-3-(6-Methoxy-1H-indol-3-yl)-indan-1-ol

Synthesis of (1*R*,3*S*)-3-(1H-indol-3-yl)-indan-1-ol (Method 4)

3mL 30% NaOMe in methanol was added to 13.49g butyric acid (1*R*,3*S*)- 3-(1H-indol-3-yl)-indan-1-yl ester in 100mL methanol. TLC showed full conversion after 1.5 hours. 1.5 g solid NH_4Cl and 50mL water were added. Methanol was removed *in vacuo* and after aqueous work up, (1*R*,3*S*)-3-(1H-indol-3-yl)-indan-1-ol (37.9 mmol) was obtained.

The following compound was synthesized in a similar way:

(1*R*,3*S*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-ol

Synthesis of (*R*)-3-(1H-indol-3-yl)-indan-1-one (Method 5)

Dess-Martin Periodane (1.08g, 2.55mmol) in 10mL CH_2Cl_2 was added to (1*S*,3*R*)- 3-(1H-Indol-3-yl)-indan-1-ol (2.52mmol) in 10mL CH_2Cl_2 at 0°C. The reaction mixture was allowed to warm to room temperature and stirred 40min - TLC showed full conversion. To the reaction mixture ethyl acetate and sat. $NaHCO_3$ was added. The organic phase was isolated, washed with 2N NaOH and brine, dried over $MgSO_4$ and concentrated *in vacuo*. A quantitative yield of (*R*)-3-(1H-indol-3-yl)-indan-1-one was obtained after flash chromatography (heptane/ethyl acetate, silica gel).

The following compounds were synthesized in a similar way:

(*R*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-one
(*S*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-one

Synthesis of 3-((1*S*,3*S*)-3-azido-indan-1-yl)-1H-indole (Method 6)

1,8-Diazabicyclo[5.4.0]undec-7-ene (4.8mL, 32.1 mmol, 1.45 equiv) was added to (1*R*,3*S*)-3-(1H-indol-3-yl)-indan-1-ol (22.2mmol) and diphenyl phosphoryl azide (6.0mL, 27.8mmol, 1.25equiv) in 150mL dry THF at 0°C. The reaction was stirred 0.5 hours at 0°C, then 2 hours at room temperature - TLC showed full conversion. The reaction mixture was poured into water and extracted with ethyl acetate. The organic phase was washed with 100mL 0.5 N HCl, sat. $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo* to give the 3-((1*S*,3*S*)-3-azido-indan-1-yl)-1H-indole.

The following compound was synthesized in a similar way:

3-((1*R*,3*R*)-3-Azido-indan-1-yl)-6-methoxy-1H-indole

Synthesis of [3-((1*R*,3*R*)-3-azido-indan-1-yl)-5-chloro-indol-1-yl]-phosphonic acid diphenyl ester (Method 7)

Diphenyl phosphoryl azide (23g, 85mmol) was added to (1*S*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-ol (10g, 35mmol) in 150mL dry THF at 5°C. 1,8-diazabicyclo[5.4.0]undec-7-ene (13.7mL, 92mmol) was added over 0.5 hours. The reaction mixture was stirred over night while warming to room temperature. The reaction mixture was poured into brine and extracted with Et_2O. The organic phase was washed with 100mL 0.1 N HCl, 0.1 N NaOH, dried over $MgSO_4$ and concentrated *in vacuo*. After flash chromatography (heptane/ethyl acetate, silica gel), 19.1g [3-((1*R*,3*R*)-3-azido-indan-1-yl)-5-chloro-indol-1-yl]-phosphonic acid diphenyl ester was isolated.

The following racemic compounds were synthesized in a similar way:

[3-(3-Azido-indan-1-yl)-indol-1-yl]-phosphonic acid diphenyl ester
[3-(3-Azido-indan-1-yl)-6-fluoro-indol-1-yl]-phosphonic acid diphenyl ester
[3-(3-Azido-indan-1-yl)-6-methoxy-indol-1-yl]-phosphonic acid diphenyl ester
[3-(3-Azido-5-fluoro-indan-1-yl)-4-chloro-indol-1-yl]-phosphonic acid diphenyl ester
[3-(3-Azido-5-chloro-indan-1-yl)-5-methoxy-indol-1-yl]-phosphonic acid diphenyl ester

Synthesis of 3-((1*R*,3*R*)-3-azido-indan-1-yl)-6-methoxy-1-(toluene-4-sulfonyl)-1H-indole (Method 8)

1g Sodium hydride (60% in mineral oil) was added to 2g 3-((1*R*,3*R*)-3-azido-indan-1-yl)-6-methoxy-1H-indole in 50 mL dry THF at 5°C and the reaction mixture was stirred 1 hour at 5°C. 2g *p*-toluene sulfonic acid chloride was added in portions at 5°C and stirring was continued for another 4 hours. Ice was added and after 1 hour water and ethyl acetate was added. The organic phase was separated and washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. After flash chromatography (heptane/ethyl acetate, silica gel), 2.5g 3-((1*R*,3*R*)-3-azido-indan-1-yl)-6-methoxy-1-(toluene-4-sulfonyl)-1H-indole was isolated.

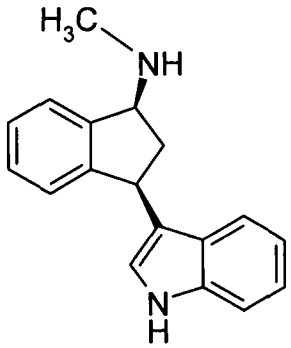
The following compound was synthesized in a similar way:

3-((1*R*,3*R*)-3-Azido-indan-1-yl)-1-(toluene-4-sulfonyl)-1H-indole

Synthesis of (1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-ylamine (Method 9)

32g Trimethyl phosphine was added over 2 hours to 19g [3-((1*R*,3*R*)-3-azido-indan-1-yl)-5-chloro-indol-1-yl]-phosphonic acid diphenyl ester in 100mL pyridine and 36mL 9N ammonium hydroxide at room temperature. The reaction mixture was stirred over night at room temperature and concentrated *in vacuo*. Ethyl acetate and water were added. The mixture was made basic with aqueous NaOH and filtered. The organic phase was concentrated *in vacuo* and was dissolved in ethyl acetate again. The ethyl acetate solution was extracted with 2x250 mL 2N methanesulfonic acid. The aqueous phase was made basic with 9N NaOH to form a precipitate, which was subjected to flash chromatography (ethyl acetate, methanol, triethylamine, silica gel) to give 0.6g (1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-ylamine. The ethyl acetate phase from above was concentrated *in vacuo* and was dissolved in 100mL methanol and 10mL 30% NaOMe in methanol was added. The reaction mixture was stirred 2 hours at room temperature, concentrated *in vacuo* and purified by flash chromatography (ethyl acetate, methanol, triethylamine, silica gel) to give further 0.45g (1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-ylamine.

Synthesis of Example 7: [(1*S*,3*R*)-3-(1H-indol-3-yl)-indan-1-yl]-methyl-amine (Method 10)

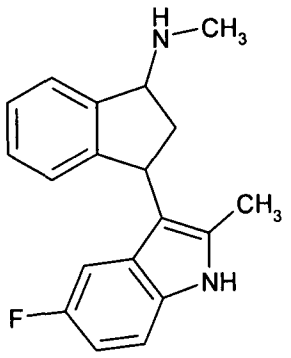


(*R*)-3-(1H-indol-3-yl)-indan-1-one, methyl amine (5mL 2M in THF) and 1mL tetraethoxy silane in 10mL methanol were stirred 11 minutes at 150°C under microwave irradiation using the Emry Optimizer™ instrument. PtO_2 (10mg) was added and the reaction mixture was stirred under 1 atm. hydrogen over night at room temperature, filtered and concentrated *in vacuo*. [(1*S*,3*R*)-3-(1H-Indol-3-yl)-indan-1-yl]-methyl-amine was isolated in 66% yield after flash chromatography (ethyl acetate, methanol, triethylamine, silica gel).

The following compounds were synthesized in a similar way:

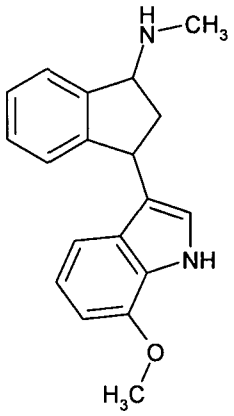
Example 1:

Racemic cis-[3-(5-Fluoro-2-methyl-1H-indol-3-yl)-indan-1-yl]-methyl-amine



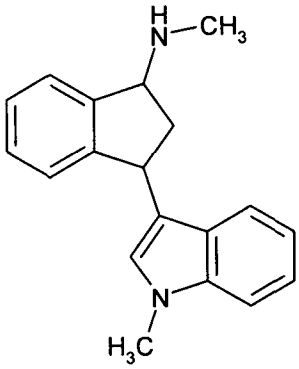
Example 2:

Racemic cis-[3-(7-Methoxy-1H-indol-3-yl)-indan-1-yl]-methyl-amine



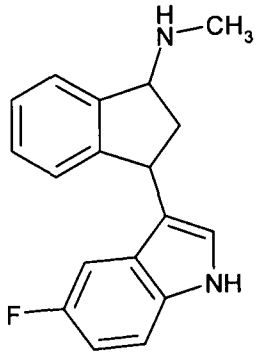
Example 3:

Racemic cis-Methyl-[3-(1-methyl-1H-indol-3-yl)-indan-1-yl]-amine



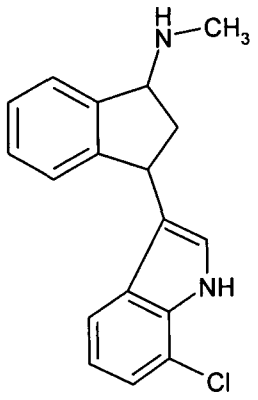
Example 4:

Racemic cis-[3-(5-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



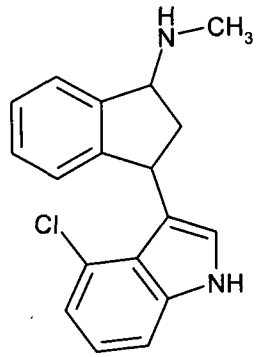
Example 5:

Racemic cis-[3-(7-Chloro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



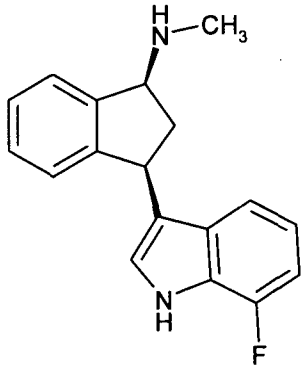
Example 6:

Racemic cis-[3-(4-Chloro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



Example 8:

[(1*R*,3*S*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



(Formula VII)

Preparative scale chiral SFC purification (Method 15): Method: Column: Chiralcel OJ-H (2 x 25 cm) operated at room temperature. Chromatography was carried out using 35 % of methanol with 0.1% (v/v) diethylamine as modifier in CO2 (100 bar) and a flow rate 50 ml/min.

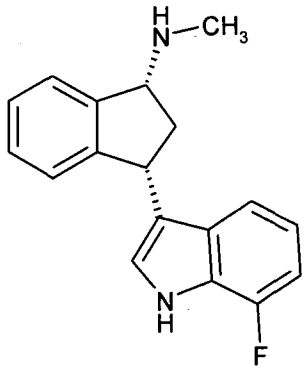
Analytical Chiral SFC: Method: Column: 250 x 4.6 mm Chiralcel AD-H with 5 μM particles operated at room temperature. Chromatography was carried out using 40 % of ethanol with 0.1% (v/v) diethylamine as modifier in CO2 (100 bar) and a flow rate 3 ml/min. Detection at 220 nm. RT_{major} = 2.52 min, RT_{minor} = 3.29 min, >99.5% ee.

LC/MS: Method A: RT = 1.85 min. UV-purity = 99.30%, ELSD purity = 96.78%

^{1}H-NMR (hydrobromide salt; d_6-DMSO): δ 2.23-2.27 (m, 1H), 2.71 (s, 3H), 2.93-2.95 (m, 1H), 4.62 (dd, *J* = 7.8Hz, 10.2Hz, 1H), 4.88 (t, *J* = 8.3Hz, 1H), 6.87-6.96 (m, 3H), 7.12 (d, *J* = 7.7Hz, 1H), 7.30 (t, *J* = 14.8Hz, 1H), 7.35-7.38 (m, 2H), 7.72 (d, *J* = 7.6Hz, 1H), 11.5 (bs, 1H).

Example 9:

[(1*S*,3*R*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



(Formula VI)

Preparative scale chiral SFC purification (Method 15): Method: Column: Chiralcel OJ-H (2 x 25 cm) operated at room temperature. Chromatography was carried out using 35 % of methanol with 0.1% (v/v) diethylamine as modifier in CO2 (100 bar) and a flow rate 50 ml/min.

Analytical Chiral SFC: Method: Column: 250 x 4.6 mm Chiralcel AD-H with 5 µM particles operated at room temperature. Chromatography was carried out using 40 % of ethanol with 0.1% (v/v) diethylamine as modifier in CO2 (100 bar) and a flow rate 3 ml/min. Detection at 220 nm. RT_{major} = 3.36 min, RT_{minor} = 2.46 min, >99.5% ee.

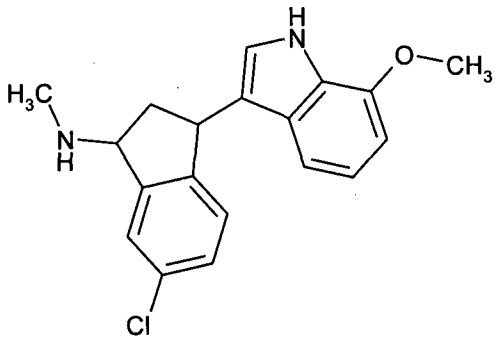
LC/MS: Method B: RT = 0.90 min. UV-purity = 99.80%, ELSD purity = 96.08%

^{1}H-NMR (d_6-DMSO): δ 1.89-1.96 (m, 1H), 2.15 (bs, 1H), 2.40 (s, 3H), 2.75-2.80 (m, 1H), 4.17 (dd, *J* = 7.3Hz, 8.7Hz, 1H), 4.44 (dd, *J* = 7.5Hz, 10.4Hz, 1H), 6.82-6.90 (m, 3H), 7.07-7.11 (m, 2H), 7.20 (t, *J* = 7.4Hz, 1H), 7.26 (d, *J* = 2.2Hz, 1H), 7.42 (d, *J* = 7.5Hz, 1H), 11.4 (bs, 1H).

^{13}C-NMR (d_6-DMSO): δ 33.7, 39.4, 63.3, 106.1 (J_{CF} = 16 Hz), 115.7, 118.5, 118.8, 124.0, 124.1, 124.3, 124.8, 124.9, 126.6, 127.2, 130.8, 145.7, 146.2, 149.7 (J_{CF} = 243 Hz).

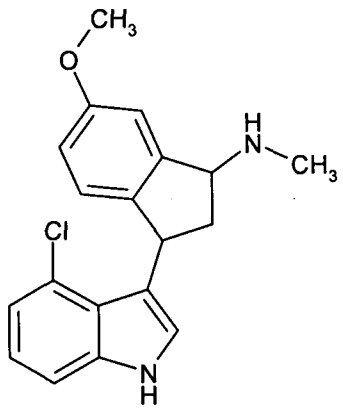
Example 11:

Racemic cis-[6-Chloro-3-(7-methoxy-1H-indol-3-yl)-indan-1-yl]-methyl-amine



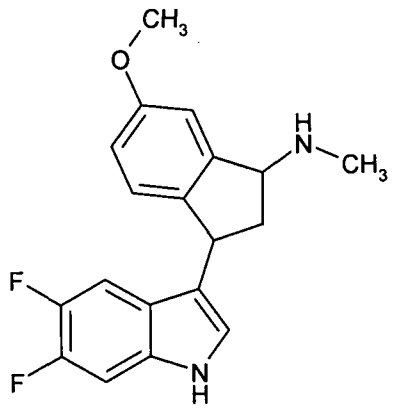
Example 12:

Racemic cis-[3-(4-Chloro-1H-indol-3-yl)-6-methoxy-indan-1-yl]-methyl-amine



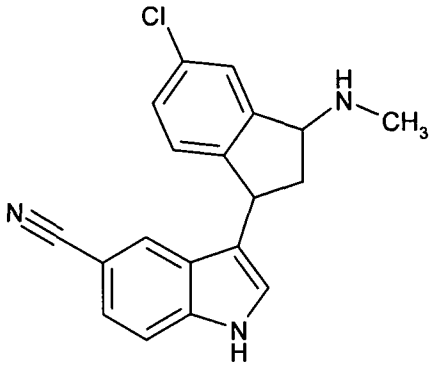
Example 13:

Racemic cis-[3-(5,6-Difluoro-1H-indol-3-yl)-6-methoxy-indan-1-yl]-methyl-amine



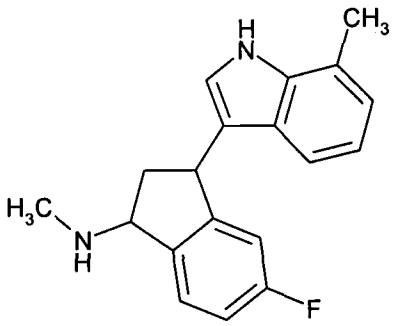
Example 14:

Racemic cis-3-(6-Chloro-3-methylamino-indan-1-yl)-1H-indole-5-carbonitrile



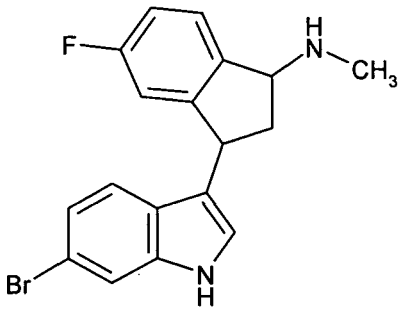
Example 15:

Racemic cis-[5-Fluoro-3-(7-methyl-1H-indol-3-yl)-indan-1-yl]-methyl-amine



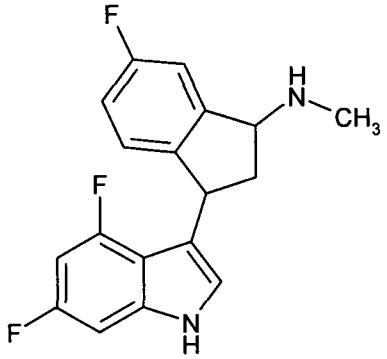
Example 16:

Racemic cis-[3-(6-Bromo-1H-indol-3-yl)-5-fluoro-indan-1-yl]-methyl-amine



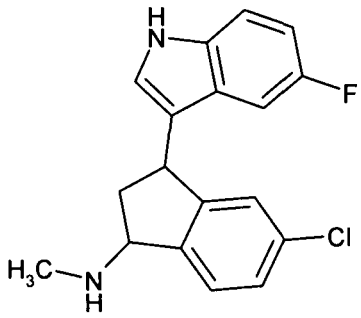
Example 23:

Racemic cis-[3-(4,6-Difluoro-1H-indol-3-yl)-6-fluoro-indan-1-yl]-methyl-amine

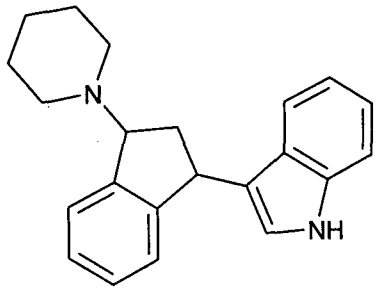


Example 24:

Racemic cis-[5-Chloro-3-(5-fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



Synthesis of Example 19: *cis*-3-(3-Piperidin-1-yl-indan-1-yl)-1H-indole (Method 11)

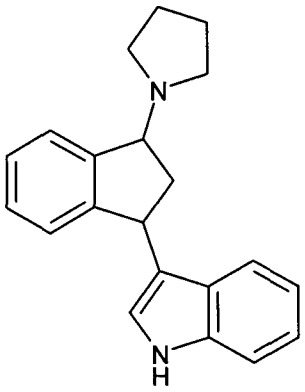


Sodium cyanoborohydride (61mg; 0.97mmol) was added to 3-(1H-indol-3-yl)-indan-1-one (200mg; 0.81mmol) and piperidine (344mg; 4.05mmol) in 3mL methanol and 0.5mL acetic acid. The reaction mixture was stirred 30 minutes at 150°C under microwave irradiation using the Emry Optimizer™ instrument. The reaction mixture was poured into water and made basic with 27% aqueous NaOH. The mixture was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. *cis*-3-(3-Piperidin-1-yl-indan-1-yl)-1H-indole was obtained after flash chromatography (ethyl acetate, heptane, triethylamine, silica gel).

The following compounds were synthesized in a similar way:

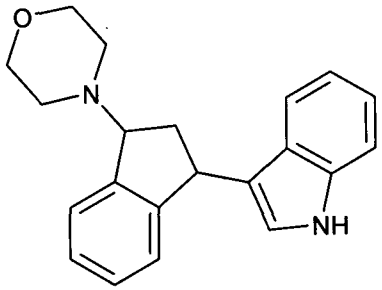
Example 20:

Racemic cis-3-(3-Pyrrolidin-1-yl-indan-1-yl)-1H-indole

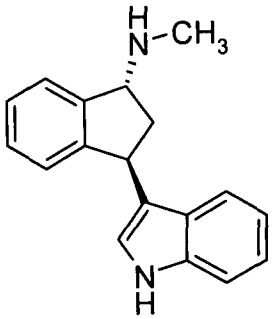


Example 21:

Racemic cis-3-(3-Morpholin-4-yl-indan-1-yl)-1H-indole



Synthesis of Example 10: [(1*R*,3*R*)-3-(1H-indol-3-yl)-indan-1-yl]-methyl-amine (Method 13)



(Formula IX)

Dimethylbromoborane (1.77mL, 1.05 equiv) (Synthesized according to Nöth, H., Vahrenkamp, H. *Journal of Organometallic Chemistry* 11(1968), 399-405) was added to 3-((1*R*,3*R*)-3-azido-indan-1-yl)-1-(toluene-4-sulfonyl)-1H-indole (17.3mmol) in 100mL 1,2-dichloro-ethane under argon at 0°C. The reaction mixture was warmed to room temperature and stirred 2.5 hours. 1mL Ethanol was added. The reaction mixture was extracted with ethyl acetate and 0.5N aqueous NaOH. The organic phase was washed with brine, dried over $MgSO_4$, concentrated *in vacuo* to give methyl-{(1*R*,3*R*)-3-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-indan-1-yl}-amine after flash chromatography (ethyl acetate, methanol, triethylamine, silica gel). Methyl-{(1*R*,3*R*)-3-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-indan-1-yl}-amine was dissolved in 8mL acetone and 20mL methanol. 8mL 28% Aqueous NaOH was added and the reaction mixture was stirred in two portions at 120°C for 10 minutes under microwave irradiation using the Emry Optimizer™ instrument. The reaction mixture was poured into 250mL water and a precipitate was formed. Recrystallization gave 2.15g [(1*R*,3*R*)-3-(1H-indol-3-yl)-indan-1-yl]-methyl-amine.

Chiral SFC: Method: Column: 250 x 4.6 mm Chiralcel OJ-H with 5 µM particles operated at room temperature. Chromatography was carried out using 30 % of 0.1%(v/v) diethylamin in ethanol as modifier, a pressure of 20 MPa and a flow rate 3 ml/min. Detection at 230 nm. RT_{major} = 2.40 min, RT_{minor} = 2.93 min, 95.9% ee.

LC/MS: Method A: RT = 1.63 min. UV-purity = 98.28%, ELSD purity = 99.61%

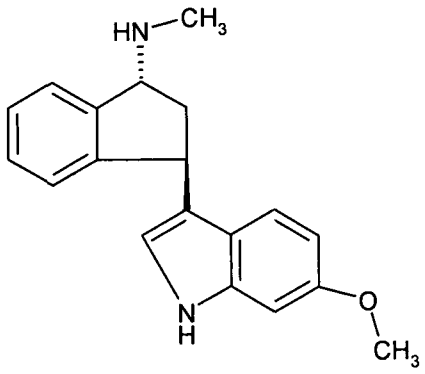
^{1}H-NMR (d_6-DMSO): δ 2.35 (m, 5H), 4.17 (dd, *J* = 3.8Hz, 6.6Hz, 1H), 4.75 (t, *J* = 7.5Hz, 1H), 6.90 (t, *J* = 7.1Hz, 1H), 7.00 (m, 3H), 7.14 (t, *J* = 7.3Hz, 1H), 7.19 (t, *J* = 7.3Hz, 1H), 7.26 (d, *J* = 8.0Hz, 1H) 7.34 (d, *J* = 7.3Hz, 1H), 7.38 (d, *J* = 7.3Hz, 1H), 10.80 (bs, 1H).

^{13}C-NMR (d_6-DMSO): δ 34.2, 39.9, 41.3, 63.6, 111.9, 118.0, 118.5, 119.1, 121.3, 122.4, 124.8, 125.0, 126.4, 126.7, 127.6, 137.1, 145.3, 147.2.

The following compound was synthesized in a similar way:

Example 27:

[(1*R*,3*R*)-3-(6-Methoxy-1H-indol-3-yl)-indan-1-yl]-methyl-amine



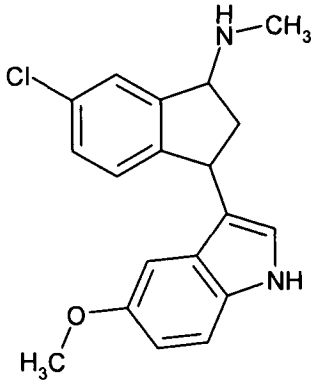
(Formula X)

LC/MS: Method A: RT = 1.60 min. UV-purity = 98.52%, ELSD purity = 99.53%

^{1}H-NMR ($CDCl_3$): δ 2.41 (ddd, *J* = 3.8Hz, 7.5Hz, 12.8Hz, 1H), 2.50 (t, *J* = 6.8Hz, 1H), 2.53 (s, 3H), 3.83 (s, 3H), 4.27 (dd, *J* = 3.8Hz, 6.8Hz, 1H), 4.79 (t, *J* = 7.5Hz, 1H), 6.72 (m, 2H), 6.85 (s, 1H), 7.2 (m, 4H), 7.40 (d, *J* = 7.3Hz, 1H), 7.82 (bs, 1H).

Synthesis of Example 25:

***Racemic trans*-[6-Chloro-3-(5-methoxy-1H-indol-3-yl)-indan-1-yl]-methyl-amine (Method 13)**

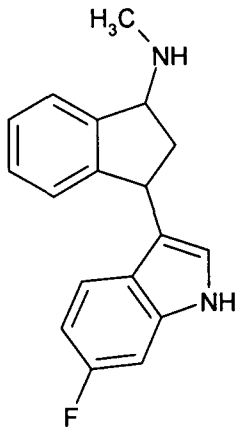


0.15 mmol Dimethylbromoborane (Synthesized according to Nöth, H., Vahrenkamp, H. *Journal of Organometallic Chemistry* 11(1968), 399-405) in 0.5 mL dry 1,2-dichloroethane was added to approximately 0.1 mmol [3-(3-Azido-6-chloro-indan-1-yl)-indol-1-yl]-phosphonic acid diphenyl ester in 2 mL dry 1,2-dichloroethane. The reaction mixture was stirred 3 hours at room temperature. The reaction was quenched by the addition of 1 mL 1 N NaOH and 1 mL brine. The mixture was extracted with ethyl acetate. The organic phase was concentrated *in vacuo*. The residue was treated with 3 mL 1M sodium methoxide in methanol for 3 h ar room temperature. 1 mL acetic acid was added and [6-Chloro-3-(1H-indol-3-yl)-indan-1-yl]-methyl-amine was isolated after preparative HPLC.

The following compounds were synthesized in a similar way:

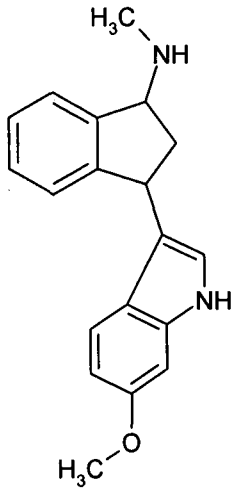
Example 17:

Racemic trans-[3-(6-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine



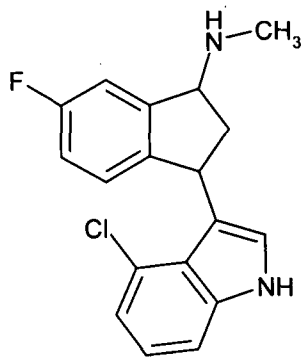
Example 18:

Racemic trans-[3-(6-Methoxy-1H-indol-3-yl)-indan-1-yl]-methyl-amine

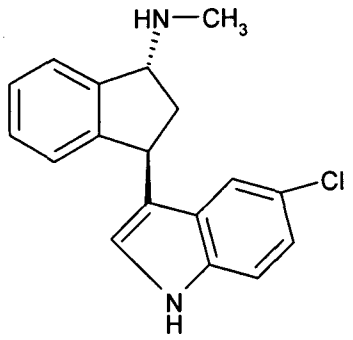


Example 22:

Racemic trans-[3-(4-Chloro-1H-indol-3-yl)-6-fluoro-indan-1-yl]-methyl-amine



Synthesis of Example 26: [(1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-yl]-methyl-amine (Method 14)



(Formula VIII)

0.73g (1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-ylamine was suspended in 200mL 1,2-dichloro-ethane, 100mL water and 0.5mL 9N NaOH. 0.25mL Methyl chloroformate (1.2 equiv) and 50mg Bu_4NBr were added. The reaction mixture was stirred 30 minutes at room temperature. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to give 0.6g [(1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-yl]-carbamic acid methyl ester. 0.6g [(1*R*,3*R*)-3-(5-Chloro-1H-indol-3-yl)-indan-1-yl]-carbamic acid methyl ester was obtained after aqueous work up. [(1*R*,3*R*)-3-(5-Chloro-1H-indol-3-yl)-indan-1-yl]-carbamic acid methyl ester was dissolved in 250mL dry THF and 0.6g $LiAlH_4$ was added. The reaction mixture was refluxed for 2 hours. The reaction was quenched with 2mL water, filtered and concentrated *in vacuo* to give an oil. The oil was dissolved in ethyl acetate and 350mg [(1*R*,3*R*)-3-(5-chloro-1H-indol-3-yl)-indan-1-yl]-methyl-amine precipitated on standing at room temperature over night.

Chiral SFC: Method: Column: 250 x 4.6 mm Chiralcel AD-H with 5 μM particles operated at room temperature. Chromatography was carried out using 30 % of 0.1%(v/v) diethylamin in ethanol as modifier, a pressure of 20 MPa and a flow rate 3 ml/min. Detection at 230 nm. RT_{major} = 2.89 min, RT_{minor} = 3.84 min, 88.6% ee.

LC/MS: Method C: RT = 1.54 min. UV-purity = 95.21%, ELSD purity = 100%

^{13}H-NMR ($CDCl_3$): δ 2.38-2.52 (m, 2H), 2.53 (s, 3H), 4.27 (dd, *J* = 3.9Hz, 6.6Hz), 4.77 (t, *J* = 7.4), 6.82 (s, 1H), 7.12 (dd, *J*= 2.0 hZ, 8.5Hz, 1H), 7.20-7.27 (m, 3H)7.37 (d, *J* = 2.0 Hz), 7.42 (d, *J* = 7.4Hz), 8.16 (bs, 1H).

Chiral separation of racemic *cis*-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl-methyl-amine (Method 15)

20 g of racemic *cis*-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl-methyl-amine (from Method 10) was purified by chiral SFC to give 9.3 g of [(1*S*,3*R*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine with >99.5% ee and 9.5 g of [(1*R*,3*S*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine with >99.5% ee.

Preparative scale chiral SFC purification method: Column: Chiralcel OJ-H (2 x 25 cm) with 5 µM particles operated at 35°C. Chromatography was carried out using 35 % of methanol with 0.1% (v/v) diethylamine as modifier in CO2 (100 bar) and a flow rate 50 ml/min.

Fractional crystallization of racemic *cis*-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl-methyl-amine with an optically active acid (Method 16)

To a solution of the racemate *cis*-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl-methyl-amine (409mg/ 2ml EtOH) was added a solution of Di-p-toluoyl-D-tartaric acid (1eq; 564mg/ 2ml Acetone). The mixture was heated to 50^0C and stirred for 15min. Evaporated the solvent and triturated with acetone (2ml). The white solid (84%ee) was collected and stirred with 10 ml hot EtOH for 30 min. The remaining white solid was collected and converted to free base to give [(1*S*,3*R*)-3-(7-Fluoro-1H-indol-3-yl)-indan-1-yl]-methyl-amine (93%ee).

Table A: Measured molecular mass ($M+H^+$), measured HPLC-retention time (R_t, min) and UV- and ELSD- purities (%).

Example No.	$M+H^+$	R_t (min.)	UV purity %	ELSD purity %	Method
1	295.2	1.82	98.6	99.9	A
2	293.2	1.79	96.7	99.2	A
3	277.2	1.91	92.5	99.9	A
4	281.1	1.78	91.5	99.6	A
5	297.1	1.94	89.7	99.6	A
6	297.1	1.98	89.3	99.6	A
7	263.1	1.66	91.1	99.6	A
8	281.1	1.85	99.3	96.8	A
9	281.0	1.89	95.2	99.5	A
10	263.1	1.64	91.9	100.0	A
11	327.1	1.97	92.9	99.9	A
12	327.1	2.02	74.5	99.3	A
13	329.1	1.94	88.0	99.7	A
14	322.1	1.83	89.2	99.9	A
15	295.2	1.93	92.2	99.1	A
16	359.0	2.07	87.7	99.4	A
17	281.1	1.77	96.8	99.6	A
18	293.2	1.75	96.2	100.0	A
19	317.1	1.85	85.1	99.0	A
20	303.1	1.82	98.3	98.9	A
21	319.0	1.72	94.3	99.4	A
22	315.1	1.88	90.2	99.8	A
23	317.1	1.89	87.8	99.3	A
24	315.1	1.90	89.3	98.6	A
25	327.1	1.89	82.7	99.3	A
26	297.2	0,94	94,5	99,4	B
27	293.1	1.60	98.5	99.5	A

TRANSPORTER INHIBITION ASSAYS

Measurements of [^{3}H]-5-HT uptake into rat cortical synaptosomes

Whole brains from male Wistar rats (125-225 g), excluding cerebellum, are homogenized in 0.40 M sucrose supplemented with 1mM nialamid with a glass/teflon homogenizer. The homogenate is centrifuged at 1000 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 40.000 x g for 20 min. The final pellet is homogenized in assay buffer (0.5 mg original tissue/well). Test compounds (or buffer) and 10 nM [^{3}H]-5-HT are added to 96 well plates. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM $CaCl_2$, 1.12 mM $MgSO_4$, 12.66 mM Na_2HPO_4, 2.97 mM NaH_2PO_4, 0.162 mM EDTA, 2g/l glucose and 0,2g/l ascorbic acid. Buffer is oxygenated with 95% 0_2/5% $C0_2$ for 10 min. The incubation is started by adding tissue to a final assay volume of 0.2 mL. After 15 min incubation with radioligand at 37 °C, samples are filtered directly on Unifilter GF/C glass fiber filters (soaked for 30 min in 0.1% polyethylenimine) under vacuum and immediately washed with 1 x 0,2 ml assay buffer. Non-specific uptake is determined using citalopram (10 µM final concentration). Citalopram is included as reference in all experiments as dose-response curve.

Measurements of [^{3}H]noradrenaline uptake into rat cortical synaptosomes

Fresh occipital-, temporal- og parietal cortex from male Wistar rats (125-225 g) are homogenized in 0.4M sucrose with a glass/teflon homogenizer. The homogenate is centrifuged at 1000 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 40.000 x g for 20 min. The final pellet is homogenized in this assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM $CaCl_2$, 1.12 mM $MgSO_4$, 12.66 mM Na_2HPO_4, 2.97 mM NaH_2PO_4, 0.162 mM EDTA, 2 g/l glucose and 0,2 g/l ascorbic acid (7,2 mg original tissue/mL = 1 mg/ 140µl). Buffer is oxygenated with 95% 0_2/5% $C0_2$ for 10 min. Pellet is suspended in 140 volumes of assaybuffer. Tissue is mixed with test compounds and after 10 min pre-incubation, 10 nM [^{3}H]-noradrenaline is added to a final volume of 0,2 ml and the mixture is incubated for 15 min at 37°C. After 15 min incubation, samples are filtered directly on Unifilter GF/C glass fiber filters (soaked for 30 min in 0.1% polyethylenimine) under vacuum and immediately washed with 1 x 0,2 mL assay buffer. Non-specific uptake is

determined using talsupram (10 µM final concentration). Duloxetine is included as reference in all experiments as dose-response curve.

Measurements of [^{3}H]dopamine uptake into rat cortical synaptosomes

Tissue preparation: male wistar rats (125-250 g) are sacrificed by decapitation and striatum quickly dissected out and placed in ice cold 0,40 M sucrose. The tissue is gently homogenised (glass teflon homogeniser) and the P2 fraction is obtained by centrifugation (1000 g, 10 minutes and 40000 g, 20 minutes, 4°C) and suspended in 560 volumes of a modified Krebs-Ringer-phosphate buffer, pH 7.4.

Tissue 0,25 mg/well(140µl) (original tissue) is mixed with test suspension. After 5 minutes pre-incubation at room temperature, 12.5 nM 3H-dopamine is added and the mixture is incubated for 5 minutes at room temperature. Final volume is 0,2 mL.

The incubation is terminated by filtering the samples under vacuum through Whatman GF/C filters with a wash of 1 x 0,2ml buffer. The filters are dried and appropriate scintillation fluid (Optiphase Supermix) is added. After storage for 2 hours in the dark the content of radioactivity is determined by liquid scintillation counting. Uptake is obtained by subtracting the non-specific binding and passive transport measured in the presence of 100 µM of benztropin. For determination of the inhibition of uptake ten concentrations of drugs covering 6 decades are used.

^{3}H-DA = 3,4-(ring-2,5,6-^{3}H)dopamine hydrochloride from New England Nuclear, specific activity 30-50 Ci/mmol.

The following references are incorporated herein by reference in their entirety:

Hyttel, Biochem. Pharmacol. 1978, 27, 1063-1068;

Hyttel, Prog. Neuro-Psychopharmacol. & bil. Psychiat. 1982, 6, 277-295;

Hyttel & Larsen, Acta Pharmacol. Tox. 1985, 56, suppl. 1, 146-153.

As shown in Table 1, activity (IC_{50}) at the monoamine transporter for the compounds in the present invention was determined to be within the range of 0.1-200 nM.

Table 1: Compound Activity at the Monoamine Transporter

	5-HTT (IC_{50} nM)	DAT (IC_{50} nM)	NAT (IC_{50} nM)
Formula VI	*	*	*
Formula VII	*	*	*
Formula VIII	*	*	*
Formula IX	*	*	*
Formula X	*	*	*
Indatraline	*	*	*
Sertraline	*	*	*

* 0.1-200 nM.

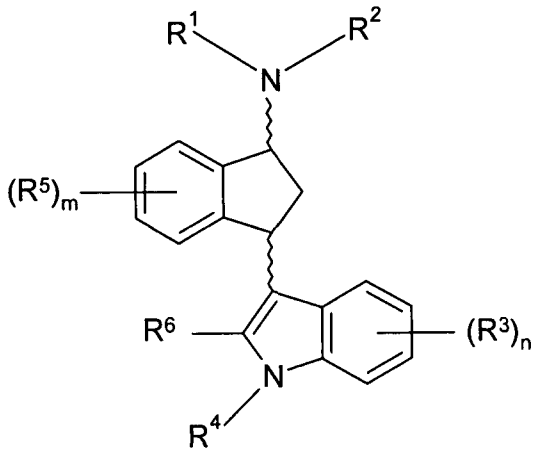
5-HTT Serotonin Transporter

DAT Dopamine Transporter

NAT Noradrenergic Transporter

What is claimed is:

1. A compound represented by the Formula I



wherein each R^1 and R^2 is independently hydrogen, C_1-C_8-straight or branched alkyl or C_3-C_8-cycloalkyl; or wherein R^1 and R^2 and the nitrogen to which they are attached form azetidine, piperidine, pyrrolidine, azapane or morpholine;

wherein each R^3 is independently hydrogen, C_1-C_8-straight or branched alkyl, C_1-C_5-alkoxy, C_1-C_8-straight or branched polyfluoroalkyl, halogen, cyano, hydroxyl, tetrazole- optionally substituted with methyl, or amino; or wherein two R^3 groups on adjacent carbons combine together to form a methylenedioxy linker;

wherein R^4 is hydrogen, C_1-C_8-straight or branched alkyl or C_3-C_8-cycloalkyl;

wherein each R^5 is hydrogen, halogen C_1-C_5-alkoxy, C_1-C_8-straight or branched alkyl, C_1-C_8-straight or branched polyfluoroalkyl, cyano, or hydroxyl;

wherein m is an integer from 1 to 4 inclusive;

wherein n is an integer from 1 to 4 inclusive; and

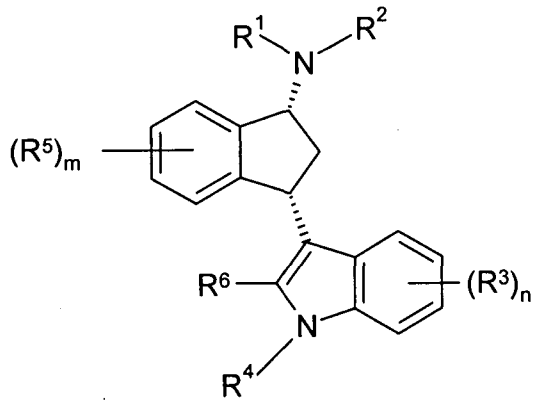
wherein R^6 is hydrogen, C_1-C_8-straight or branched alkyl or phenyl;

or pharmaceutically acceptable salts thereof.

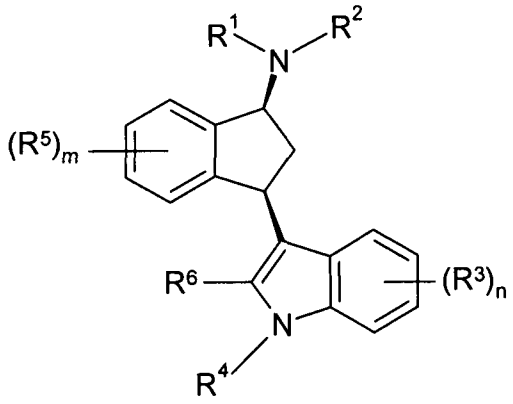
2. The compound of claim 1, wherein the compound is the cis isomer.

3. The compound of claim 1, wherein the compound is the trans isomer.

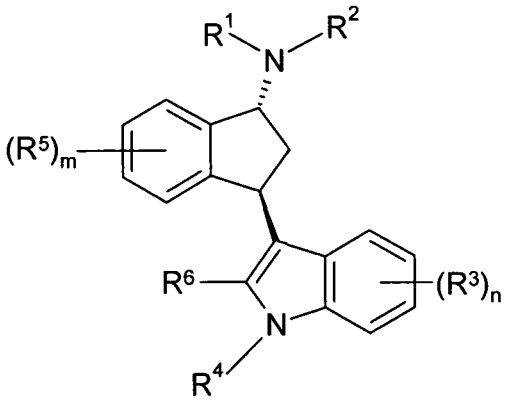
4. The compound according to Claim 1 of Formula II-V selected from the group consisting of:



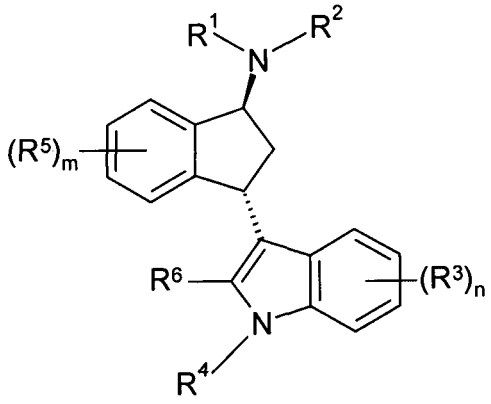
(II);



(III);



(IV); and



(V).

5. The compound of Formula II, III, IV or V according to Claim 4, wherein R^1 is hydrogen.

6. The compound of Claim 5, wherein R^2 is methyl.

7. The compound of Claim 6, wherein R^4 is hydrogen.

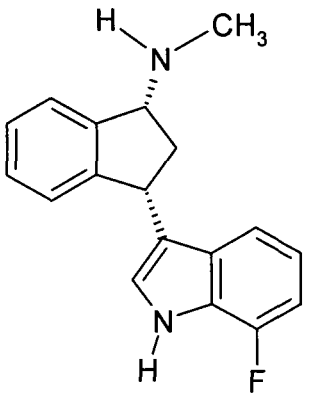
8. The compound of Claim 7, wherein R^3 is selected form the group consisting of hydrogen, halogen, and methoxy.

9. The compound of Claim 8, wherein R^3 is a hydrogen or halogen.

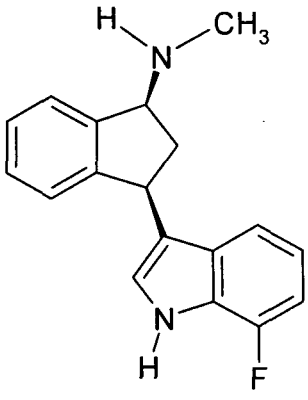
10. The compound of Claim 9, wherein the halogen is fluorine or chlorine.

11. The compound of Claim 10, wherein R^5 and R^6 are hydrogen.

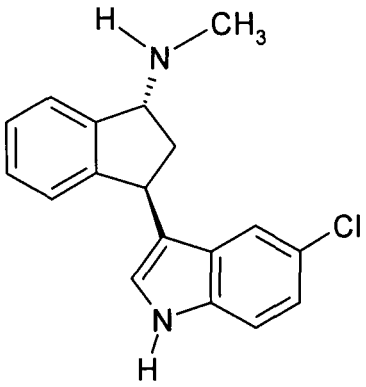
12. A compound selected from the group consisting of:



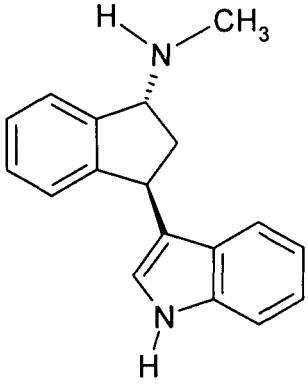
(VI);



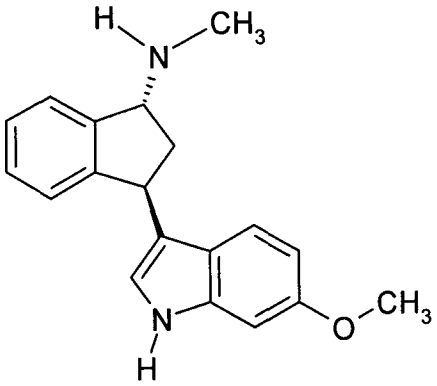
(VII);



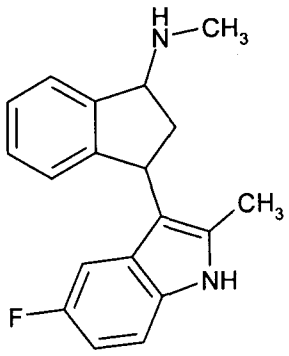
(VIII);



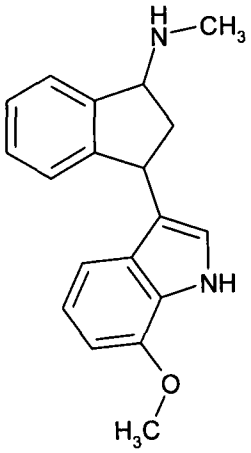
(IX);



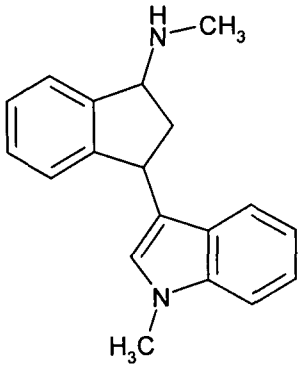
(X);



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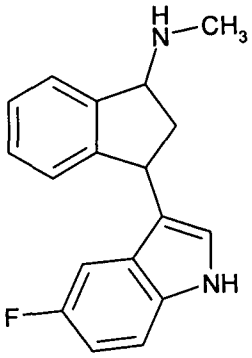


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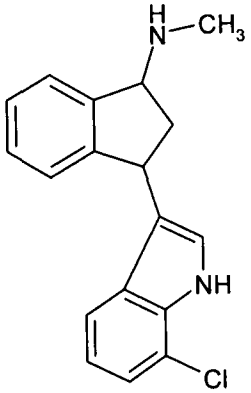


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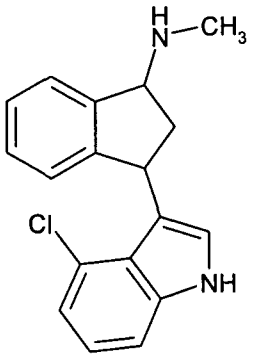
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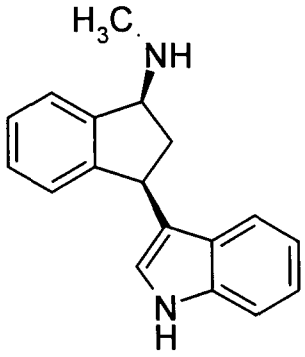
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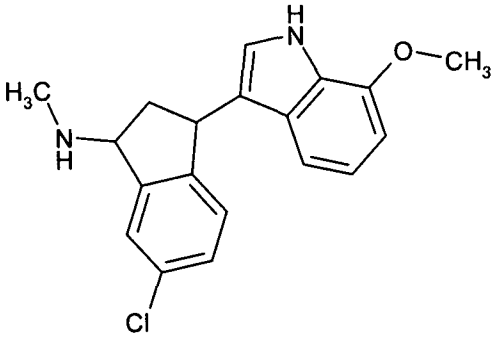
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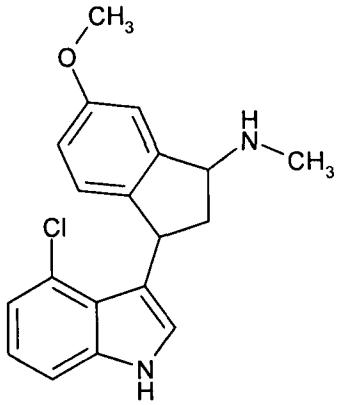
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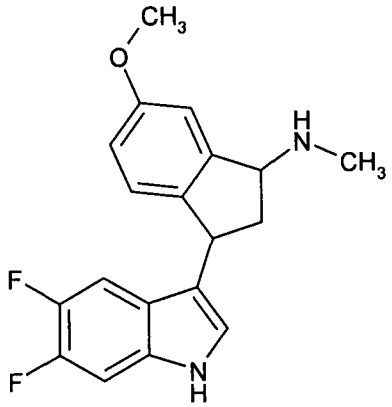


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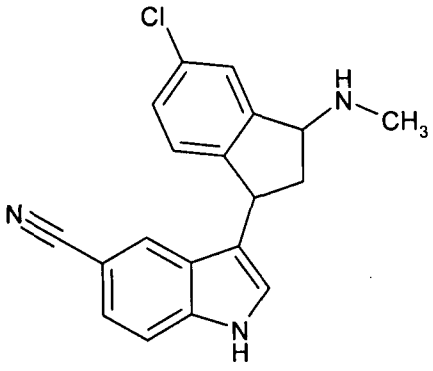


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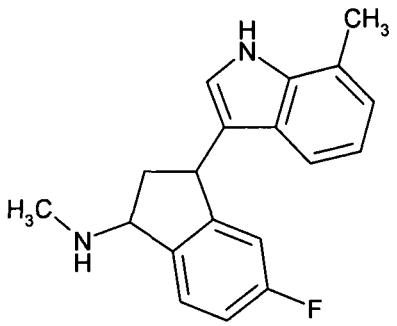
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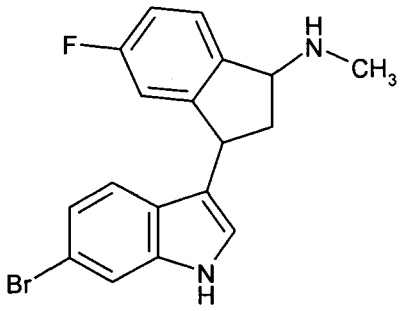


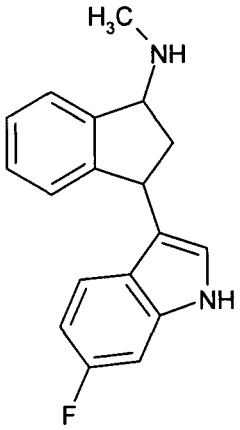
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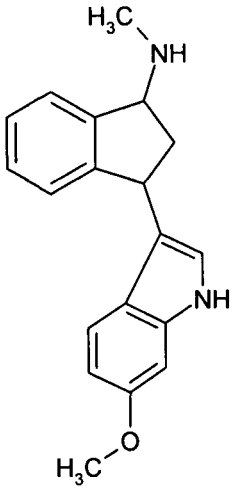


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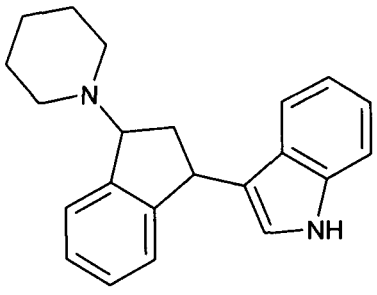

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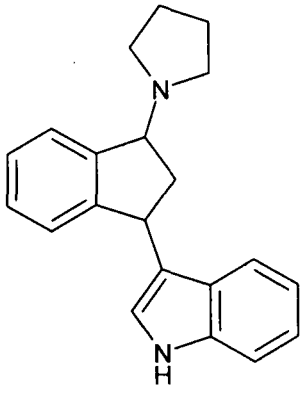

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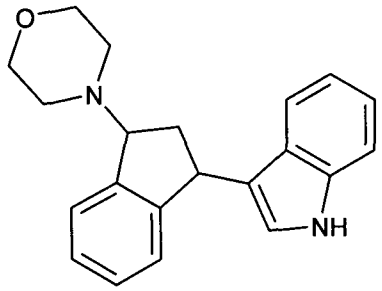

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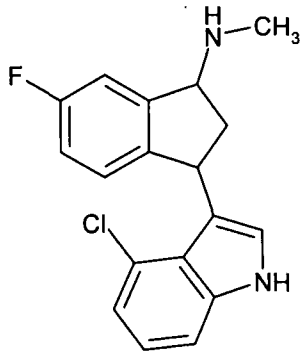

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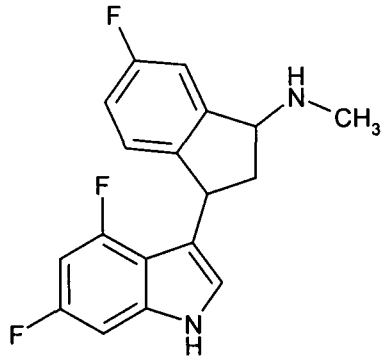
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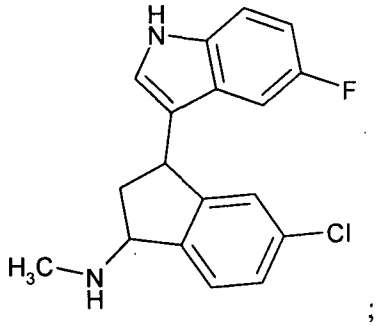

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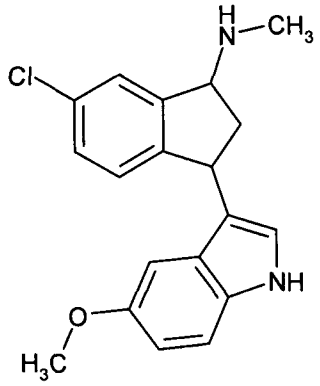

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or a pharmaceutically acceptable salt thereof.

13. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any one of Claims 1, 2, 3, 4 and 12 and a pharmaceutically acceptable carrier.

14. A method for the treatment of affective disorders, pain disorders, attention deficit hyperactivity disorder (ADHD), cognitive disorders, substance abuse, smoking cessation and stress urinary incontinence in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of Claims 1, 2, 3, 4 and 12.

15. The method of Claim 14, wherein the affective disorder to be treated is selected from the group consisting of depressive disorders and anxiety disorders.

16. The method of Claim 15, wherein the depressive disorder to be treated is selected from the group consisting of major depressive disorder, melancholia, postnatal depression, dysthymia, depression associated with bipolar disorder, depression associated with Alzheimer's disease, depression associated with psychosis, and depression associated with Parkinson's disease.

17. The method of Claim 15, wherein the anxiety disorder to be treated is selected from the group consisting of general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and agoraphobia.

18. The method of Claim 14, wherein the pain disorder to be treated is selected from the group consisting of fibromyalgia syndrome (FMS), overall pain, back pain, shoulder pain, headache, pain while awake and pain during daily activities.